A Phase 1/2 Trial of BKM120 Combined with Vemurafenib (PLX4032) in BRAF$^{V600E/K}$ Mutant Advanced Melanoma

Protocol Number: CC #11952
Study Drug: BKM120

Version Number: 8.0
Version Date: June 24, 2013

IND Number: 113646

Novartis study number CBKM120ZUS21T

Principal Investigator

Alain Algazi, MD (PI)
University of California, San Francisco
1600 Divisadero Street
Mt. Zion Building A, Room A739
San Francisco, CA 94143-1770
Phone: (415) 353-7552
Pager: (415) 443-0409
Cell: (415) 418-8039
Email: *alain.algazi@ucsf.edu*
Fax: (415) 353-7999

Co-Investigators

Adil Daud, MD (Co-PI)
University of California, San Francisco
1600 Divisadero Street
Mt. Zion Building A, Room A741
San Francisco, CA 94143-1770
Phone: (415) 353-7392
Pager: (415) 443-2233
Email: *adil.daud@ucsf.edu*
Fax: (415) 353-9956

Revision History

Amendment 8	June 24, 2013
Amendment 7	March 22, 2013
Amendment 6	September 28, 2012
Amendment 5	April 27, 2012
Amendment 4	March 22, 2012
Amendment 3	November 8, 2011
Amendment 2	October 11, 2011
Amendment 1	August 23, 2011
Initial Protocol	July 26, 2011

Protocol Signature Page

Protocol No.: **Version Date:**June 24, 2013

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators‟ Brochure (or Manufacturer‟s Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Participating Site(s)

PI: StergiosMoschios, MD
University of North Carolina at Chapel Hill
Physician Office Building
170 Manning Drive, Chapel Hill, NC 27599

PI: Karl Lewis, MD
University of Colorado
Anschutz Cancer Pavilion
1665 Court Room, 32 Aurora, CO 80045

Principal Investigator **Site**

_____ _____
Printed Name

_____ _____
Signature Date

Table of contents

Appendices

List of Abbreviations

AE	Adverse Event
AKT	See PKB (protein Kinase B)
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BRAF	B-RAF seronine / threonine kinase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHR	UCSF Committee for Human Research (IRB)
CK	Creatine Kinase
CK-MB	Creatine Kinase - Muscle and Brain isoenzyme
CR	Complete Response
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
EGFR	Epidermal Growth Factor Receptor
ERK	ERK extracellular signal-regulated kinase
18F-FDG	[18F]-Fluorodeoxyglucose
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
HDL	High density lipoprotein
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low density lipoprotein

List of Abbreviations

LVEF	Left Ventricular Ejection fraction
MRI	Magnetic Resonance Imaging
MEK	MEK mitogen activated protein kinase
MUGA	Multiple Gated Acquisition Scan
NTD	Non-Tolerated Dose
PD	Pharmacodynamic
PET	Positron Emission Tomography
PI3K	Phosphatidylinositol 3‟-kinase
PK	Pharmacokinetic
PKB	Protein Kinase B (or AKT)
PT	Prothrombin Time
PTEN	Phosphatase and Tensin homolog
PTT	Partial Thromboplastin Time (also known as APTT)
QTc	QT interval (corrected)
RBC	Red Blood Cells
REB	Research Ethics Board
RP2D	Recommended Phase 2 Dose
RECIST	Response Evaluation In Solid Tumors
S6K	Protein Kinase S6
SAE	Serious adverse event
SOP	Standard Operating Procedure
SUV	Standardized Uptake Value
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Count
WCBP	Women of Childbearing Potential

Background

1.1 Disease Background – Overview

In 2010 over 60,000 patients were diagnosed with melanoma in the US and over 8,000 died from this disease[1]. Despite many advances in oncology, the prognosis of metastatic melanoma remains dismal[2], and melanoma is highly refractory to standard chemotherapy. A better understanding of melanoma biology and rational development of targeted therapies is urgently needed. The identification of tumor driving oncogenes now promises to revolutionize the treatment of melanoma. Mutations in the BRAF seronine-threonine kinase leading to constitutive activation of the MAP kinase pathway occur in over half of melanoma tumors and over 90% of these mutations results in a substitution of either glutamic acid or lysine for valine at amino acid 600 ($BRAF^{V600E}$ or $BRAF^{V600K}$)[3,4]. Vemurafenib(also cited in the literature under the names PLX4032, RO5185426, and RG7204)is a potent BRAF inhibitor that induces objective tumor responses in half of $BRAF^{V600E/K}$ mutant advanced melanoma cases, but these responses are transient, with a median PFS of 5.3 months in phase 3 testing[5]. The limitations of vemurafenib are not surprising given that $BRAF^{V600E/K}$ mutations alone do not cause melanoma. BRAF mutations are common in benign nevi[6] and animal studies suggest that BRAF must cooperate with additional oncogenic mutations to yield a malignant phenotype[7]. Constitutive PI3 kinase pathway activation, often in the setting of PTEN mutations, is common in melanoma cell lines and melanoma metastases, particularly those harboring BRAF mutations[8,9]. While BRAF mutations alone cannot induce melanoma, a BRAF mutation combined with PI3K pathway activation is sufficient to transform melanocytes in preclinical models[7]. In such models, inhibition of either the MAP kinase or PI3 kinase pathway leads to tumor growth inhibition *in vivo*, and concurrent inhibition of *both* pathways is synergistic leading to tumor regression.

Given this and the evidence supporting the role of PI3K activation in the malignant melanoma phenotype in $BRAF^{V600E/K}$ mutant melanoma tumors, the limitations of BRAF-specific therapies may stem from the failure to block constitutive PI3K signaling. Indeed, PTEN loss, which increases PI3K activity, was recently identified a predictor of decreased progression free survival in $BRAF^{V600E}$ melanoma patients treated with vemurafenib[10]. BKM120 is a potent, orally bioavailable PI3K inhibitor that that induces marked reductions in PI3K pathway activity in patients with advanced solid tumors[11]. This is a phase 1/2 clinical trial with the goal of determining whether the addition of BKM120 to vemurafenib will lead to clinically significant improvements in 6-month progression free and in $BRAF^{V600E/K}$ mutant melanoma.

1.2 Vemurafenib(PLX4032, RO5185426, RG7204)

Vemurafenib is a highly selective oral, ATP-competitive inhibitor of the mutant $BRAF^{V600E/K}$serinine/threonine kinase. Vemurafenib inhibits the mutated $BRAF^{V600E}$ and $BRAF^{V600K}$ kinases at low nanomolar concentrations *in vitro* with minimal activation of other kinases at concentrations less than 100 nM with the exception of ACK1, KHS1, and SRMS[12]. Vemurafenib and related compounds potentiate MAP kinase signaling the cells that are wild type for BRAF[13,14].

1.2.1 Vemurafenib preclinical studies

1.2.1.1 Vemurafenib preclinical efficacy

Vemurafenib demonstrates *in vitro* and *in vivo* efficacy in cell lines and xenografts that are homozygous or heterozygous for sensitive BRAF mutations, but it does not demonstrate anti-tumor activity in BRAF wild-type tumors[12,15,16]. In $BRAF^{V600E}$ mutant colorectal cancer xenograft (COLO205) studies in mice, vemurafenib induced dose-dependent tumor growth inhibition with tumor regression at higher doses[12]. At doses of 25 mg/kg bid 7 of 10 animals achieved a complete response and 3 of 10 had partial responses.

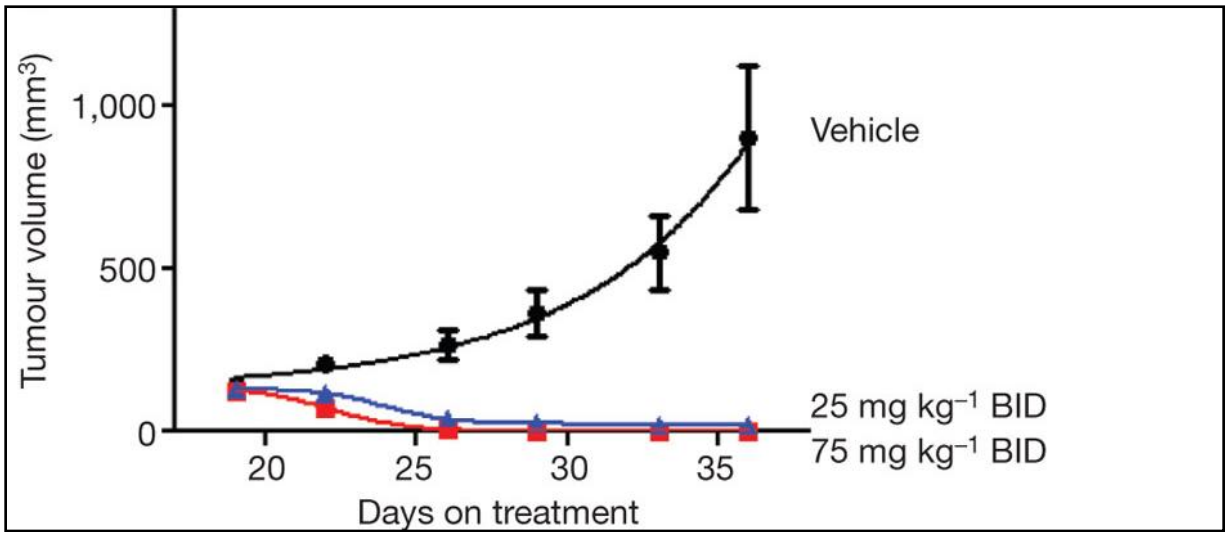


Figure 1. Tumor response as a function of time in mice treated with vemurafenib dosed twice daily at two dose levels compared with animals treated with vehicle control (n = 10 in each group) [12]**.**

At doses of50 mg/kg bid, 10/10 animals had CRs. Significant tumor regressions were noted in mice at doses of 20 mg/kg bid (AUC_{0-24} approximately 300µMh) in several $BRAF^{V600E}$xenograft models including COLO205, NCI-LOX, and COLO829[12].

Vemurafenib demonstrated similar efficacy in murine xenograft models of $BRAF^{V600E}$ mutant melanoma[15]. Complete tumor regressions were observed in 5/9 LOX xenograft mice treated at 12.5 mg/kg and partial regressions were seen in the remaining four animals (*Figure 2A*). Complete regressions were observed of 10/10 LOX xenograft mice treated with doses of 25 and 75 mg/kg. Dose-dependent improvements in survival were also noted (*Figure 2B*). In an A375 murine xenograft model, initial dosing at 75 mg/kg followed by dosing at 25 mg/kg yielded improvements in survival in comparison with vehicle controls to continuous dosing at 75 mg/kg[15].

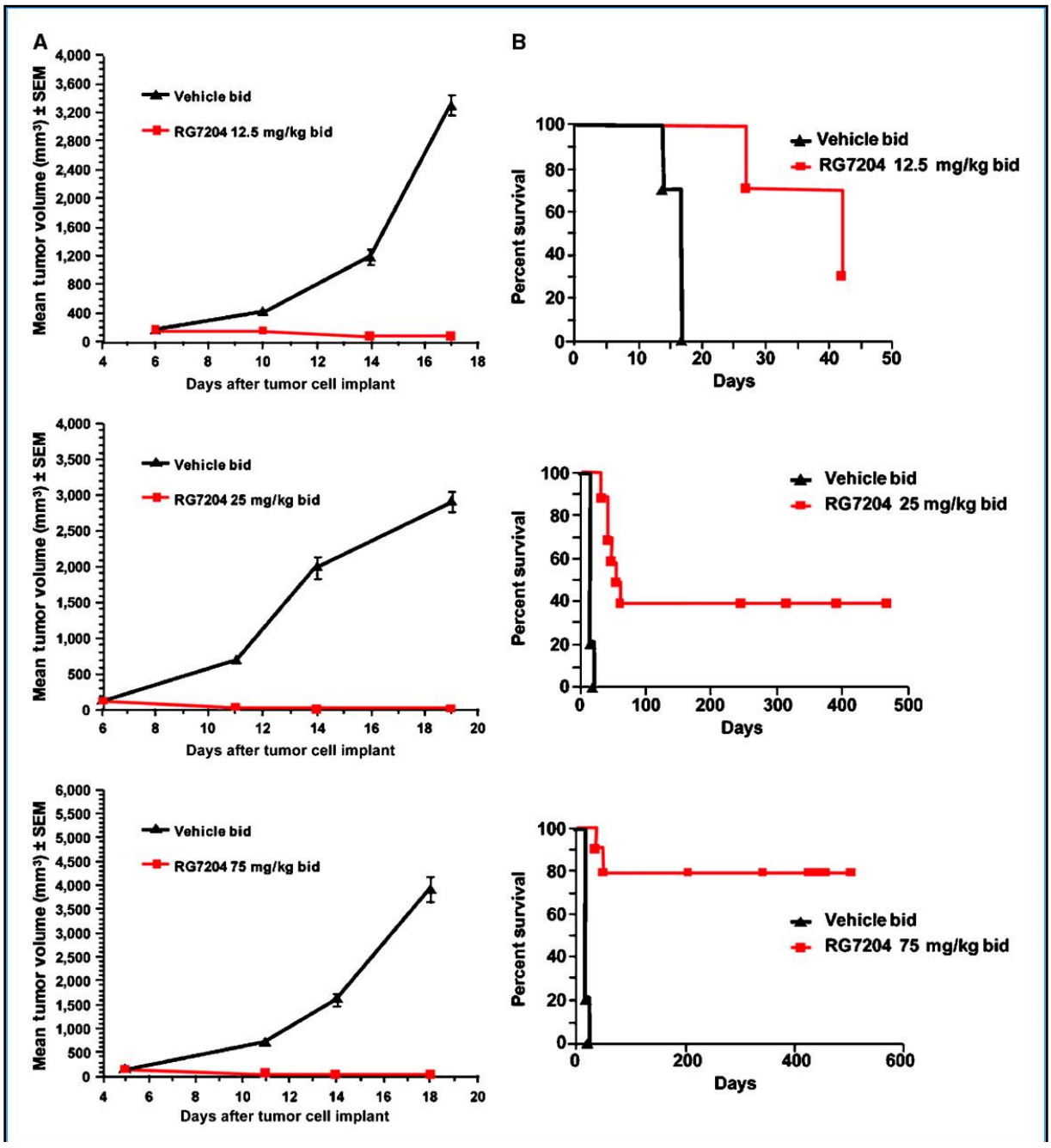


Figure 2.Vemurafenib inhibits tumor growth and prolongs survival in a BRAF^{V600E}-bearing LOX melanoma xenograft model. Groups of mice were treated with vemurafenib administered bid at doses of 12.5, 25, and 75 mg/kg for 11 to 13 d starting on day 5 to 6 after implantation. A, efficacy data are plotted as mean tumor volume (in mm^3) ± SEM. B, survival data are plotted as percent of animals surviving in each group using a predefined cutoff volume of 2,000 mm^3 as a surrogate for survival[15].

1.2.1.2 Vemurafenib preclinical safety

No toxicity was observed in rats and dogs receiving doses of up to 1,000 mg/kg/day of vemurafenib for 28 days. Extended dosing over 13 weeks in dogs and 26 weeks in rats was tolerable despite high overall exposure levels of 820 mMh and 2,600 mMh in dogs and rats respectively. In particular, no histological changes were seen in the animals" skin in any of these studies[12]. There was also no toxicity observed in a mouse xenograft study at doses of up to 100 mg/kg and drug exposures up to an AUC of 3810 μMh[15].

1.2.1.3 Vemurafenib preclinical pharmacology

In a melanoma mouse model, single doses of vemurafenib of 100 mg/kg yielded a peak plasma concentration of 124 mmol/l at 2 hours while a peak intratumoral concentration of 37.8 mmol/L were observed at 4 hours (*Figure 3*)[15].Pharmacodynamic analysis by Western Blot revealed stable pMEK inhibition of 64.8% until 8 hours post-dose, and maximum pERK inhibition of 52% at 2 hours. These phosphoprotein levels were thought to be underestimated due to stromal contamination. At time points (T_{max}) ranging from 2-4 hours, continuous dosing of the microprecipitated bulk powder formulation of vemurafenib yielded peak concentrations (C_{max}) of 68.4, 139, 164, and 196 μM at doses of 25, 50, 75, and 100 mg/Kg respectively. The total drug exposures (AUC) were 1250, 2340, 3070, and 3810 μMh respectively. In a murine colorectal carcinoma xenograft model using a less bioavailable formulation of vemurafenib, the AUC_{0-24} was approximately 50, 200, and 300 μMh at doses of 6 mg/kg daily, 20 mg/kg daily, and 20 mg/kg bid respectively[12].

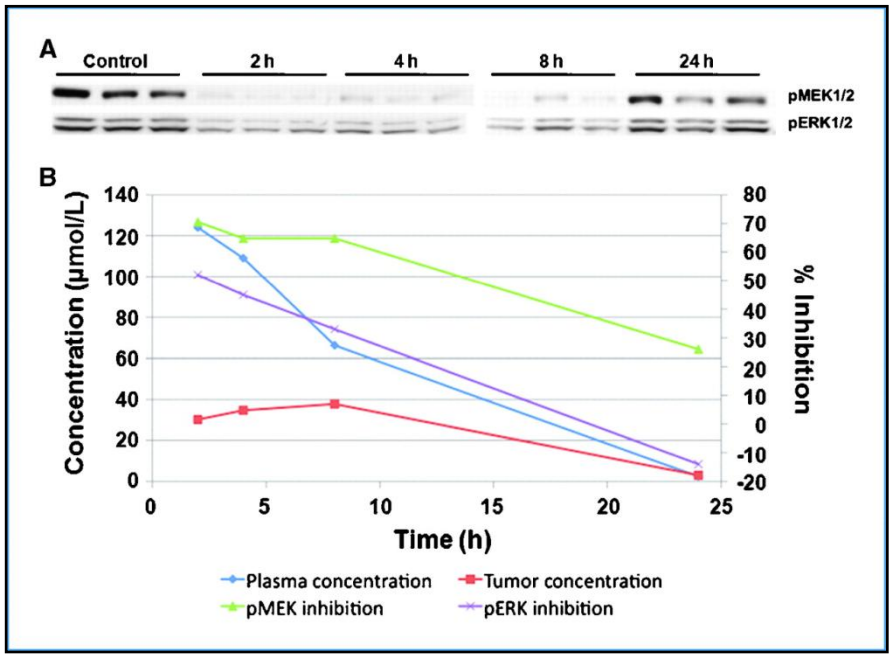


Figure 3.PD and PK relationship of vemurafenib in the LOX melanoma xenograft model. Plasma and tumor samples were obtained at 2, 4, 8, and 24 h post dose for PD and PK analysis from mice administered a single dose of 100 mg/kg vemurafenib orally when tumors were ~300 mm^3. A, tumor samples were subjected to Western blot analysis with antibodies specific for pMEK1/2 and pERK1/2. B, mean PD and PK parameters were calculated from

three animals analyzed at each time point and plotted as a function of time post dose. Vemurafenib plasma and tumor concentrations are plotted on the left Y-axis. Inhibitions of MEK1/2 and ERK1/2 phosphorylation are plotted on the right Y-axis[15].

Vemurafenib undergoes minimal hepatic metabolism, primarily through CYP3A4. Vemurafenib is a mild inducer of CYP3A4, and an inhibitor of CYP2C9, CYP1A2, CYP2C19, CYP2D6, and P-gp. In addition, vemurafenib induces mild to moderate increases mRNA expression of CYP3A4 and CYP1A2.

1.2.2 Vemurafenib clinical experience

1.2.2.1 Vemurafenib clinical efficacy

A phase 3 clinical trial presented at the plenary session of the 2011 ASCO Annual Meeting and in the New England Journal of Medicine demonstrated that vemurafenib is superior to standard-of-care dacarbazine in terms of clinical response rate (48 vs. 5%), median progression-free survival (5.3 vs. 1.6 months), and 6 month overall survival (84 vs. 64%)[5]. Additional trials of vemurafenibinclude a phase 1 dose-escalation trial with an extension cohort at the phase 2 study dose, a phase 2 trial, a study of the effect of food on the metabolism of vemurafenib, and an additional phase 1 pharmacokinetic study to test a micro-precipitated bulk powder (MBP) form of vemurafenib in tablets that has replaced an MBP product in capsules. In the original phase 1 study[4], 49 melanoma patients (and 6 patients without melanoma) were enrolled in a dose escalation phase and 32 additional patients, all with $BRAF^{V600E}$ mutant melanoma were enrolled in a dose expansion phase. In the dose escalation phase, the maximum administered dose (MAD) was 1120 mg PO bid. At this dose level, four of six patient developed dose limiting toxicities (DLTs, 3 with grade 3 rash, 1 with grade 3 arthralgias). The recommended phase 2 dose identified was 960 mg PO bid. No responses were seen in melanoma patients whose tumors did not harbor the $BRAF^{V600E}$ mutation. In the dose escalation phase, 10/16 patients receiving doses of 240 mg PO bid or more of vemurafenib had partial tumor responses and 1 had a complete response. In the expansion phase, 24/32 patients had partial responses and 2 had complete responses. Notably, objective tumor responses were not confirmed in the data presented in the published report, and the confirmed response rate has been reported as 59%[17]. The median PFS was approximately 7 months. The phase 2 trial enrolled 132 patients, and as of 9/27/2010, the confirmed response rate was 52% with 3/132 CRs and 66 PRs. 39 additional patients had stable disease. The median PFS was 6.2 months, and the median response duration was 6.8 months[17].

1.2.2.2 Vemurafenib safety

Common grade 2 or higher drug-related adverse events of vemurafenib include rash, photosensitivity, pruritis, palmar-plantar dysesthesias, squamous cell carcinomas of the skin/keratoacanthomas, fatigue, nausea, and arthralgias[4,5]. In 87 patients in the phase 1 trial, only four patients had grade 4 adverse events potentially related to vemurafenib: two had GGT elevations, one had fatigue, and one had pancytopenia. No deaths were associated with treatment with vemurafenib. 32 patients on this trial were treated in an extension cohort at the recommended phase 2 dose of 960 mg PO bid. 13 (41%) of these patients required dose reductions for adverse events. In 10 of these patients, a dose of 720 mg PO bid was well tolerated, one was dose-reduced to 600 mg PO bid, and two ultimately received 480 mg PO bid.

Table 1. Drug-related adverse events of grade 2 or higher reported in more than 5% of 618 phase 3 study patients receiving vemurafenib or dacarbazine[5]

Adverse Event	Vemurafenib (N=336)†	Dacarbazine (N=282)
	no. of patients (%)	
Arthralgia		
Grade 2	60 (18)	1 (<1)
Grade 3	11 (3)	2 (<1)
Rash		
Grade 2	33 (10)	0
Grade 3	28 (8)	0
Fatigue		
Grade 2	38 (11)	33 (12)
Grade 3	6 (2)	5 (2)
Cutaneous squamous-cell carcinoma‡		
Grade 3	40 (12)	1 (<1)
Keratoacanthoma§		
Grade 2	7 (2)	0
Grade 3	20 (6)	0
Nausea		
Grade 2	25 (7)	32 (11)
Grade 3	4 (1)	5 (2)
Alopecia		
Grade 2	26 (8)¶	0
Pruritus		
Grade 2	19 (6)	0
Grade 3	5 (1)	0
Hyperkeratosis		
Grade 2	17 (5)	0
Grade 3	4 (1)	0
Diarrhea		
Grade 2	16 (5)	4 (1)
Grade 3	2 (<1)	1 (<1)
Headache		
Grade 2	15 (4)	5 (2)
Grade 3	2 (<1)	0
Vomiting		
Grade 2	9 (3)	14 (5)
Grade 3	4 (1)	3 (1)
Neutropenia		
Grade 2	1 (<1)	4 (1)
Grade 3	0	15 (5)
Grade 4	1 (<1)	8 (3)
Grade 5	0	1 (<1)

* Listed are all adverse events of grade 2 or higher that were reported in more than 5% of patients in either study group.
† One patient in the dacarbazine group who was treated with vemurafenib in error was included in the vemurafenib group for the assessment of adverse events.
‡ The criteria for the diagnosis of cutaneous squamous-cell carcinoma were defined in the protocol and were reported as grade 3, according to the National Cancer Institute Common Terminology Criteria for Adverse Events. These events were evaluated by the investigators as grade 1 in one patient and as grade 2 in one patient.
§ Three patients with keratoacanthomas that were assessed by the investigator as grade 1 are included among the grade 2 keratoacanthomas.
¶ In one patient, alopecia that was scored as grade 3 by the investigator was rescored as grade 2 since the Common Terminology Criteria for Adverse Events do not include grade 3 alopecia.

The emergence of secondary keratoacanthomas and other secondary squamous cell carcinomas of the skin were of particular concern. The median time to appearance of these lesions was 8 weeks. All were treated with local excision and no treatment interruptions were required. No other secondary malignancies were observed. Additional adverse event data from the recently-completed phase 3 trial are given in ***Table 1***.

1.2.3 Vemurafenib clinical pharmacology

In phase 1 testing, exposure to vemurafenib in the MBP formulation increased proportionally to dose for doses ranging from 240 mg PO bid to 960 mg twice daily[4]. 24-hour exposure (AUC_{0-24}) at the recommended phase 2 dose was 1741±639 mMh and the maximum concentration at steady state was 86±32 μM. The estimated half-life of vemurafenib was approximately 50 hours (range 30-80 hours), and all patients were exposed to relativelyconstant daily drug levels at the steady state with twice daily dosing. Vemurafenib has very low aqueous solubility and > 99.5% of the drug is bound to plasma protein[12].

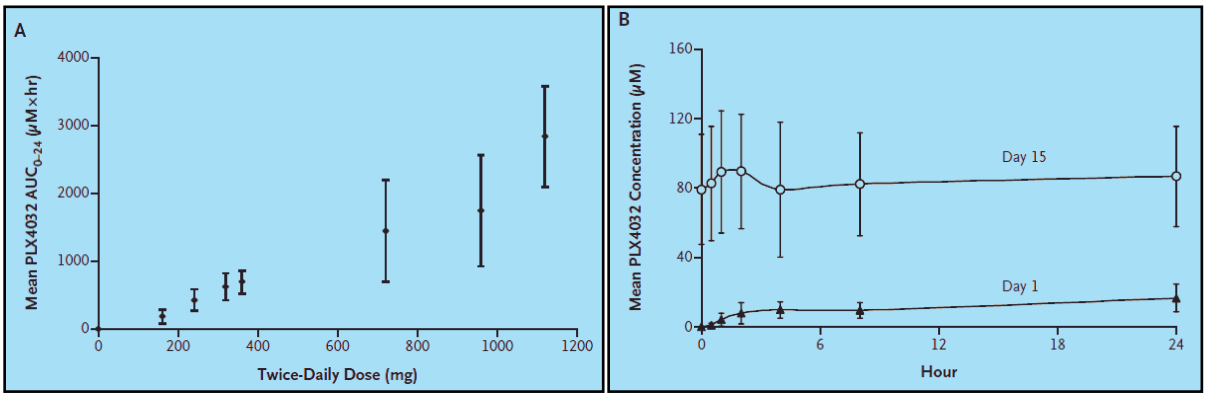


Figure 4. Panel A – mean AUC_{0-24} for vemurafenib with twice daily dosing. Panel B – mean concentration of vemurafenib after the administration of a single dose on day 1 or multiple doses at the steady state on day 15 at the recommended phase 2 dose of 960 mg PO bid. I bars indicate standard deviations.

Paired biopsy specimens revealed marked reductions in tumor levels of phosphorylated ERK, cyclin D1 and Ki-67 at day 15 at dose levels of 240 mg PO bid or higher[4,12] indication marked inhibition of the MAPkinase pathway.

1.3 BKM120

NVP-BKM120 (BKM120) is an oral pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2,6-dimorpholino pyrimidine derivative family. The eight members of the PI3K family have been classified into three classes: Class I PI3Ks are key players in the PI3K-PDK1-AKT pathway, which regulates cell proliferation, growth, survival and apoptosis. In many tumors the PI3K signaling pathway is constitutively activated. This is thought to be a critical step in mediating the transforming potential and growth stimulating activity of various oncogenes (ErbB2, EGFR, p53, Ras, Src, etc.) contributing to the onset and growth of solid tumors as well as hematological tumors.

1.4 PI3K Pathway and mechanism of action

PI3K signaling is a hallmark of many cancers. Subsets of cancers become also dependent on PI3K pathway signaling ("pathway addicted")[18] as a result of mutations of the PIK3CA gene itself or of regulators of PI3K (e.g. PTEN, HER2). As a consequence, pathway mutated tumors are particularly sensitive towards PI3K-pathway inhibition.

The superfamily of PI3 kinases is characterized by primary sequence homologies within the catalytic domain of these enzymes. Currently, 8 members of this family are known, belonging to three classes (I-III). At structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. PI3K signaling regulates diverse cellular functions, including protein synthesis and glucose metabolism, cell survival and growth, proliferation, cellular resilience and repair, cell migration, and angiogenesis[19]. PI3K is negatively regulated at the level of PIP3 by phospholipids phosphatases, such as the phosphatase and tensin homologue PTEN and the inositol 5′ phosphatase-2 SHIP2. In addition, signaling through the PI3K pathway is modulated by crosstalk with other signals and pathways, including hormones (estrogen, thyroid hormones), vitamins, integrins, intracellular calcium and the Ras-dependent MAPK pathway.

Constitutive activation of PI3K signaling is deemed to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and, in many tumors, the PI3K pathway is constitutively activated. Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers. Several lines of evidence suggest that inhibition of the PI3K signaling pathway might provide benefit for the treatment of many cancers: solid tumors (breast cancer, prostate cancer, glioblastomamultiforme, colon cancer, lung cancer etc.) and tumors of the hematopoetic system[20-29].

The molecular changes leading to constitutive activation of the PI3K pathway are diverse and fall into four categories: (1): Gain-of-function mutations of oncogenes encoding positive regulators of PI3K (HER2, EGFR, ras, c-src), including oncogenes coding for components of PI3K itself (PIK3CA that codes for the subunit p110α, gene coding for p85) (2): Loss-of function mutations affecting negative regulators of PI3K such PTEN (i.e. loss of PTEN expression or function)[30,31] (3): Mutations of genes encoding downstream effectors of the PI3K signaling cascade (e.g. PDK-1, Akt/PKB, RPS6KB1) (4): Mutation of the tumor suppressor p53 (i.e. that regulates PI3K signaling through repression of PIK3CA).

1.4.1 BKM120 preclinical studies

BKM120 activity against class I PI3K (p110α, -β, -δ and -γ), Class III (Vps34), the class IV mTor related PI3K or PI4Kβ, was assessed using either using a luciferase luminescence (class I or III PI3Ks and PI4Kβ) or a TR-FRET assay (Class IV mTor). The IC50 in these assays is outlined below in *Table 2*.

Table 2.Inhibitory activities (IC50) of BKM120 against other PI3K or related kinases

Assay	IC_{50} (nM ± SD)	Assay	IC_{50} (nM ± SD)
p110α	0.035 ± 0.017	Vps34	2.41 ± 1.5
p110α-H1047R	0.058 ± 0.002		
p110α-E545K	0.099 ± 0.006	mTor	4.61 ± 1.86
p110α-E542K	0.084 ± 0.001		
p110β	0.175 ± 0.067	PI4Kβ	>25
p110δ	0.108 ± 0.048		
p110γ	0.348 ± 0.013		

All the IC50s (expressed in µM ± SD) were determined as described in the method report [RD-2007-00365], using a KinaseGlo® (PI4Kβ and Vps34) or TR-FRET assay format (mTor).

BKM120 significantly inhibits p110α and the most common p110α mutations (H1047R, E454K, E542K), p110β, p110δ and p110γbut not the related proteins Vps34, mTor or PI4Kβ. Hence BKM120 is classified as a pure pan-class I PI3K inhibitor. Enzymatic characterization of the inhibitory properties of the compound revealed that BKM120 is a mixed inhibitor of PI3Kα with a strong competitive component (largest on Vmax). The cocrystal X-ray structure of BKM120 with PI3Kγ confirmed that BKM120 interacts with PI3K into the ATP catalytic cleft.

The PI3K pathway regulates the activity of the mTORC1 complex, when cells are challenged through mitogenic stimuli. In order to assess in cells the potential impact of the BKM120 on the mTORC1 complex, the compound was tested in TSC1 null cells. These cells express a constitutively activated mTORC1 complex that uncouples the mTor pathway from the PI3K upstream input[32]. When exposed to TSC1 null MEFS, BKM120 reduced the S235/236P-RPS6 levels with an IC50 of 1785 nM, in agreement with the data obtained in the mTor biochemical assay. In contrast, and as expected the allosteric mTORC1 inhibitor RAD001 displayed sub-nanomolar inhibitory activity in this assay.

In contrast to molecules with distinct mechanism of action (BCR-Abl inhibitor STI571, mTORC1 allosteric inhibitor RAD001), BKM120 is able to decrease the phosphorylation status of various either direct (GSK3β, FKHRL1/FOXO3a) or indirect downstream Akt effectors (p70S6K, through mTor) in the PTEN null U87MG cell line, as efficiently as prototypical PI3K inhibitors such as LY294002 and Wortmannin.

Forkhead transcription factors (such as FKHRL1) are re-located from the nucleus to the cytosol upon phosphorylation by Akt. Treatment of U2OS cells stably expressing GFP - FKHRL1 chimera to GFP with BKM120 produced a strong nuclear localization of the fluorescence signal, in agreement with the reduction of the phosphorylated FKHRL1 levels. Signaling pathways from membrane receptors to nuclear transcription factors involve many different players such as kinases or molecular adaptors. To test whether BKM120 does influence other signaling molecules outside of the PI3K pathway, induction of various pathways (mitogenic with EGF and PDGF, stress pathways with anisomycine and interleukine pathways with IL-4) were interrogated in the presence of the compound. In all cases, BKM120 showed specific PI3K pathway attenuation, as demonstrated by specific attenuation of S473P-Akt levels, without affecting the non PI3K driven read –outs such as activated receptors (EGFR, PDGFR), MAPK kinases (ERK, JNK and p38) or Jak cytosolic tyrosine kinases responsible for Stat transcription factor phosphorylation.

Preclinical Safety

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted *in vitro* and *in vivo*, did not indicate a prominent electrophysiological risk. In the isolated rabbit heart, effects pointing towards a shortened repolarization were seen only at 10 μM. BKM120 inhibited hERG channel activity significantly at concentrations ≥ 100 ∝M (IC_{50}: 190 ∝M). No relevant electrophysiological effect was seen in dogs. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, observed in two dog telemetry studies.

Repeated-dose studies (up to 13 weeks of duration) were performed in rats and dogs. In rats, clinical pathology and histopathology findings showed a decrease in lymphocyte counts in the peripheral blood, decreases in germinal center development in different lymph nodes, and lymphocytolysis in the thymus. In dogs, similar findings occurred. In both species, erythropoiesis was affected, as evidenced by reduced erythrocyte counts, accompanied by bone marrow depression observed in rats.

The pancreas was seen to be affected by treatment with BKM120, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. In addition, in one of the four recovery animals minimal acinar cell atrophy was observed after four weeks treatment-free period. In rats, in the 4-week study, no pancreas toxicity was observed (however, in the 2-week dose range finding study, at higher doses, there were histopathological findings of the endocrine as well as the exocrine pancreas).

Male sexual organs and associated tissues were found to be targets of toxicity in both rats and dogs. Changes included minimal to slight germ cell depletion, formation of spermatic giant cells and abnormal spermatids, and cellular debris in epididymal tubules. Testicular toxicity did not fully reverse after the 4-week treatment-free period in rats (highest dose) although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles; in addition, an increased incidence of diestrus stage of the estrous cycle was seen. In dogs, there was no effect on female sexual organs.

Insulin/glucose homeostasis was impacted in various species (mice, rats, dogs), as expected from the mode of action of BKM120. However, in both rats and dogs, at the doses used in the 4-week studies, these effects were minimal.

After up to 2 weeks of treatment with up to 2.5 mg/kg/day, decreased levels of glutamate, dopamine, serotonin and epinephrine as well as elevated levels of glutamine, GABA (gamma-amino butyric acid) and HIAA (5-hydroxyindoleacetic acid, a serotonin breakdown product) were seen in rats. The increased levels of HIAA and decreased levels of serotonin indicate an increased serotonin breakdown, pointing to a potential perturbation of the serotonin release and/or re-uptake. Generally, the decreased levels of glutamate, dopamine, serotonin and epinephrine points to an exhaustion of these neurotransmitters. No such effects were seen in cerebrospinal fluid (CSF) or plasma of those animals.

Both in vitro and in vivo, BKM120 elicited a genotoxic potential. While no evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro, a potential for genotoxicity was concluded based on the observation of an aneugenic potential, seen in this latter experiment. In line with this result, BKM120 treatment resulted in an elevated

frequency of micronucleated polychromatic erythrocytes in the bone marrow of rats.

In conclusion, the majority of the observed effects were related to the pharmacological activity of BKM120 as an inhibitor of PI3K, such as a potential influence on glucose/insulin homeostasis and the risk of increased blood pressure. Main target organs of toxic effects were bone marrow and lymphoid tissue, pancreas, and male as well as, to a lesser extent, female reproductive organs. Further, neurotransmitter fluctuations were seen in the brain of rats, not visible in plasma or cerebrospinal fluid.

Please refer to the Investigator‟s Brochure for additional information on the preclinical testing of BKM120.

1.4.1.1 Pharmacodynamics

BKM120 inhibits wild-type PI3Kα (IC50: 35 nM), with at least 50 fold selectivity towardprotein kinases. The compound is equipotent against somatic PI3Kα mutations (H1047R-,E542K- and E545K-p110α) and is active against the other three PI3K paralogs (PI3Kβ, -γ, -δ;108 to 348 nM range). BKM120 does not significantly inhibit the related kinases mTor andVps34, nor does it inhibit (IC50 >10 μM) other receptors and ion channels profiled.BKM120 reduces the phosphorylation of direct downstream effector Akt in mechanistic andrelevant tumor cell lines (IC50: 93 nM for S473P-Akt in Rat1-p110α cells). This biologicalactivity correlates with inhibition of various Akt downstream signaling pathway componentsand with its anti-proliferative activity against a variety of tumor cell lines. Our data suggestthat response to BKM120 in breast cancer cell lines is associated with HER amplificationand/or PIK3CAmu. The role of PTEN loss-of-function as predictor of response seems to beless clear.

BKM120 demonstrated significant tumor growth inhibition in tumor xenografts of a variety ofcancer types in mice and rats, including several models of breast cancer. In particular,BKM120 showed high anti-tumor activity and synergism when combined with trastuzumab inthe HER2-amplified breast cancer model BT474 (as well as in the Her2-amplified gastricmodel NCI-N87). In vivo PK/PD analyses of tumor tissues showed a good correlationbetween exposure, PI3K pathway blockade (S473P-Akt levels) and anti-tumor activity.

1.4.1.2 Preclinical Pharmacology, Pharmacokinetics and Metabolism

BKM120 was rapidly absorbed with a good oral bioavailability in all animal species tested.The compound has a moderate plasma CL and Vss. BKM120 is moderately bound to plasmaprotein across all species examined and widely distributed to most tissues in the rat. Drugrelated radioactivity enters the brain and testes, and has an affinity to melanin containingtissues. No unique, major phase 1 metabolites were identified in human hepatocytes. BKM120and metabolites have a low potential for covalent binding to protein. BKM120 is not asubstrate for nor an inhibitor of P-glycoprotien (MDR-1) or Multidrug Resistance Related Protein 2 MRP2. The compound is also not an inhibitor of Breast Cancer Resistance Protein (BCRP).

With respect to potential drug-drug interactions, at 100 mg qd BKM120 is predicted to be a weak reversible inhibitor of CYP3A4 (K_i 13.6 μM, 0.1 < I/Ki <1). BKM120 also weakly inhibited the CYP2C family (2C8, 2C9 and 2C19) with IC_{50} values ranging from 35-65 μM (34-59 μM unbound). BKM120 shows no apparent time dependent inhibition of CYP1A2, CYP2C9,

CYP2D6 or CYP3A4/5. Oxidative metabolism of BKM120 was found to be predominantly mediated by CYP3A4 (estimated fm> 0.9), with only minor contributions of CYP1A1. Hence, BKM120 is a sensitive CYP3A4 substrate and there is potential for drug-drug interactions with co-medications that are inhibitors or inducers of CYP3A4. It is possible that BKM120 may activate PXR in vivo and induce CYP3A4 at concentrations ≥ 50 μM. The potential for drug-drug interactions between BKM120 and vemurafenib based on their hepatic metabolism is summarized in *Table 3*.

Table 3. The metabolism of vemurafenib and BKM120 by hepatic microsomes

Vemurafenib undergoes minimal hepatic metabolism, primarily by CYP3A4, and BKM120 is a weak CYP3A4 inhibitor. BKM120 undergoes significant metabolism by CYP3A4. Vemurafenib increases CYP3A4 mRNA expression and is a mild CYP3A4 inducer.

	PLX4032	***BKM120***
Metabolized/ Transported by	**CYP3A4** Minimal hepatic metabolism P-gp (weak)	**CYP3A4 (major; fm>0.9)** CYP1A1 (minor)
Metabolites	Eight	None
Induces	**CYP3A4 (mild)**	Potential induction of 3A4 @ ≥50uM
Inhibits	CYP2C9 CYP1A2 CYP2C19 CYP2D6 P-gp	**CYP3A4 (weak, reversible, Ki 13.6mM)** CYP2C8 (weak, 35-65mM) CYP2C9 CYP2C19
Increased mRNA expression	**CYP3A4 (weak to moderate)** CYP1A2	

1.4.2 BMK120 clinical experience

1.4.2.1 BKM120 Pharmacokinetics and pharmacodynamics

Pharmacokinetic data observed so far showed that BKM120 is rapidly absorbed after oral administration with mean peak plasma concentrations (C_{max}) ranging between 0.5 to 4 h post dose (t_{max}). The median t_{max} at the MTD dose (100 mg daily) was about 1 hour. After reaching C_{max}, BKM120 plasma concentrations decreased in a bi-exponential manner. Apparent total body clearance from plasma (CL/F) was low: ~5.0 L/h, indicating that BKM120 is a low clearance drug. BKM120 accumulated ~3-fold in achieving steady-state, consistent with an effective half-life of ~40 h. Steady-state can be expected to be reached after approximately 7-10 days of daily dosing in most patients. Approximate dose-proportional increase in $C_{max}$and AUC was found in the dose range of 12.5-150 mg. Intersubject variability in C_{max} and AUC differed at each dose level but was relatively low and generally around 40%. Doses of 50mg/day and above led to steady-state drug exposure (AUC0-24,.SS) > 10,000 ng*h/mL, a target efficacious exposure level estimated preclinically.

Due to the difficulty to obtain fresh tumor tissue during treatment, pharmacodynamic measurements were limited to surrogate tissues such as skin and blood. The parameters assessed have been selected for their relevance to PI3K/mTOR signaling modulation: phosphorylated S6 ribosomal protein in the skin (S6 is a well known downstream target ofmTOR/PI3K pathway) and C-peptide and glucose levels in the blood (PI3K/mTOR signaling has a critical role in glucose metabolism). A formal analysis of these assessments is currently ongoing. Consistent suppression of S6 activation in skin was evident at the highest doses tested (100 and 150mg/day) with 30 to 80% decrease from baseline levels. Occasional increases of C-peptide have been seen at all doses, while hyperglycemia was one of the DLTs suggesting potential impairment of glucose transport and utilization by the tissues (insulin resistance).

More information is provided in the BKM120 Investigators‟ Brochure.

1.4.2.2 Clinical experience with BKM120

As of 20th August 2010, a total of 80 patients were enrolled and received at least one BKM120 treatment among whom 75 patients [in trials CBKM120X2101 (N=66) and CBKM120X1101(N=9)] received BKM120 treatment in monotherapy setting and 5 patients [in trials CBKM120B2101 (N=4) and CBKM120X1107 (N=1)] received BKM120 in combination settings.

In monotherapy setting, 6 dose levels have been explored: 12.5 mg/d (N=1), 25 mg/d (N=5), 50 mg/d (N=8), 80 m/d (N=11), 100 mg/d (N=46), and 150 mg/d (N=4). For combination therapy, BKM120 has been tested so far with GSK1120212 [CBKM120B2101 (N=4)] and trastuzumab [CBKM120X2107 (N=1)] at 30 mg/d and 50 mg/d respectively.

Seven dose-limiting toxicities (DLTs) were observed in CBKM120X2101: 2 patients with grade 4 hyperglycemia (150mg/d); 1 patient withgrade 3 upper abdominal pain, 1 patient with grade 3 skin rash, 1 patient with grade 2 mood alteration, 1 patient with grade 3 mood alteration (100mg/d); and 1 patient with grade 2 mood alteration (80 mg/d). The maximum tolerated dose (MTD) for BKM120 single agent study was defined as 100 mg/d in Dec 09. As of 20- Aug-10, one DLT, grade 4 liver function abnormal, has been observed in CBKM120X1101; and no DLT has yet been observed in BKM120 combination studies CBKM120B2101 and CBKM120X2107. The MTD in BKM120X1101 (for Japanese patient population) and combination therapy has not been determined yet.

The largest clinical experience is based on an ongoing Phase 1 first-in-man study of single-agent oral BKM120, CBKM120X2101. The study has been designed as a Bayesian Logistic Regression dose-escalation trial with a MTD dose-expansion arm enrolling patients with advanced solid tumors. Patients, who are pre-selected for molecular alterations of PI3K and/or PTEN gene, are currently being enrolled in the MTD expansion arm to further characterize the safety, PK and PD profile of BKM120 at the MTD dose. Overall the treatment has been generally well tolerated.

As of 20-Aug-10, the most common adverse events in CBKM120X2101($\geq$ 15%) regardless of grade and causalitywere decreased appetite (45.5%), nausea (39.4%), constipation, diarrhea, fatigue (each 31.8%), rash (30.3%), hyperglycemia (27.3%), asthenia (25.8%), abdominal pain,

vomiting (each 22.7%), anxiety (21.2%), depression (19.7%), mucosal inflammation, pruritus (each18.2%), dyspnea (16.7%), AST increase, dry skin, dyspepsia, pyrexia, and somnolence (each 15.2%).The CTCAE grade 3 or 4 adverse events suspected to be BKM120 treatment related (with a frequency > 2%) included increased transaminases (total 13.6%, with overlappedtransaminitis, AST increase and ALT increase as 7.6%, 3.0%, 3.0% respectively), rash (6.1%), hyperglycemia (4.5%), diarrhea, pruritus, depression, mood altered, and affective disorder (each 3.0%).Newly or worsened CTCAEgrade 3 and4 abnormalities (≥ 15%) in blood biochemistry included AST increase (20.6%) and ALT increase (15.9%). Newly or worsened CTCAEgrade 3 and 4 hematologic abnormalities (≥ 15%) were limited to low absolute lymphocytes (19.1%).Thirty three out of 66 patients (50.0%) experienced at least one QT alteration.No patient had new QTcF or QTcB> 500 msec and/or increased from baseline > 60 msec. New clinically meaningful ECG abnormalities (≥ 15%) included sinus tachycardia (23.1%), sinus bradycardia, and atrial premature contractions (APC) (each 16.7%).Nine deaths were reported, as of 20-Aug-10, and all were due to disease progression. The common adverse events leading to study discontinuation, regardless of study drug relationship, were hyperbilirubinemia and hyperglycemia (each 3.0%).Please refer to the BKM120 Investigators Brochure for safety profile detail of first-in-human trial CBKM120X2101.

To date, the safety profiles of study [CBKM120X1101(N=9), CBKM120X2017 (N=1), and CBKM120B2101 (N=4)], look similar to the safety profile of BKM120 in study CBKM120X2101. Further data are being collected, the overall safety profile is subject to change. Based on the observed safety profile, clinicians using BKM120 should pay special attention to significant adverse events related to liver function abnormalities as recently reported.

In the first-in-humans study, CBKM120X2101, forty-five (45) patients to date are evaluable for efficacy assessed both with Computed Tomography (CT) scan and 18-Fluorodeoxyglucose-Positron Emission Tomography (^{18}F-FDG PET) scan. Two RECIST partial responses have been observed. Twenty-six patients (58%) had a stable disease as best response. With regards to the PI3K pathway activation, of the two responders described above, one had a tumor with the PIK3CA mutation. Moreover, 8 out 18 patients had a stable disease lasting for 16 weeks or longer had tumors with an activated PI3K pathway.Please refer to the Investigator‟s Brochure for additional information on the available clinicalexperience with BKM120.

1.5 Study Rationale

Mutations in the BRAF seronine-threonine kinase leading to constitutive activation of the MAP kinase pathway occur in over half of cutaneous melanoma tumors[3]. Vemurafenibis a potent BRAF inhibitor that induces objective tumor responses in the majority of $BRAF^{V600E/K}$ mutant advanced melanoma cases, but these responses are transient, lasting approximately 6 months[4,12]. The limitations of vemurafenib are not surprising given that $BRAF^{V600E/K}$ mutations alone do not cause melanoma. BRAF mutations are common in benign nevi[6] and animal studies suggest that BRAF must cooperate with additional oncogenic mutations to yield a malignant phenotype [7]. Constitutive PI3 kinase pathway activation, often in the setting of PTEN mutations, is common in melanoma cell lines and melanoma metastases particularly those harboring BRAF mutations[8,9]. While BRAF mutations alone cannot induce melanoma, BRAF mutation combined with PI3K pathway activation is sufficient to transform melanocytes in preclinical models [7].

Based on the premise that PI3K activation is necessary to maintain the malignant melanoma phenotype in $BRAF^{V600E/K}$ mutant melanoma tumors, this trial will test the hypothesis that the limitations of BRAF-specific therapies frequently stem from the failure to block constitutive PI3K signaling. BKM120 is a potent, orally bioavailable PI3K inhibitor that that induces marked reductions in PI3K pathway activity in patients with advanced solid tumors[11]. This is a phase 1/2 clinical trial with the goal of determining whether the addition of BKM120 to vemurafenib will lead to improved 6-month progression-free survival in $BRAF^{V600E/K}$ mutant melanoma.

2 Study Objectives

Primary

Phase 1
*Part A:*Determine the recommended phase 2 dose (RP2D) of the PI3K pan class I alpha inhibitor BKM120 when administered in combination the BRAF inhibitor vemurafenib in BRAF inhibitor naïvepatients with $BRAF^{V600E/K}$ mutant melanoma.

*Part B:*Determine the recommended phase 2 dose (RP2D) of the PI3K pan class I alpha inhibitor BKM120 when administered in combination the BRAF inhibitor vemurafenib in patients with $BRAF^{V600E/K}$ mutant melanoma who were previously treated with a BRAF inhibitor.

Phase 2
Determine the 6-month progression-free survival rate (PFS6) in patients with $BRAF^{V600E/K}$ positive advanced melanoma treated with BKM120 in combination withvemurafenib.

Secondary

Phase 1
Determine the pharmacokinetics (PK) of BKM120 administered alone and in combinationwith vemurafenib in Part A (BRAF inhibitor naïve patients with $BRAF^{V600E/K}$ mutant melanoma) and in Part B ($BRAF^{V600E/K}$ mutant melanoma who were previously treated with a BRAF inhibitor).

Phase 2
1. Determine the objective response rate, (ORR = CR + PR), PFS and OS for $BRAF^{V600}$ mutant advanced melanoma patients treated with BKM120 in combination withvemurafenib.

2. Determine the safety and tolerability associated with BKM120 in combination withvemurafenib in patients with $BRAF^{V600E/K}$ positive advanced melanoma.

3. Determine whether pre-treatment PTEN expression is associated with better progression-free survival.

4. Determine whether greater reduction in PI3K-pathway signaling is associated with better progression-free survival.

5. i. Determine whether responding tumors lack gene expression signatures of both PI3K and MAPK pathway activation.ii. Determine whether progressing tumors demonstrate gene expression signatures of either PI3K or MAPK pathway activation.

3 Study plan

3.1 Overall study design

Phase 1

Part A

The phase 1portion of this trial is a 3+3 dose escalation study. In *Part A* ofthe phase 1 portion of the study, there will be a 7 day lead-in period (cycle 0) to allow for single dose pharmacokinetic analysis of BKM120 alone. Patients will receive continuous dosing of vemurafenib and BKM120 starting on cycle 1, day 1 (See *Figure 5*, Study design). Cycle 1 (28 days) will be defined as the DLT period.

Part B

In *Part B* of the phase 1 portion of the study, there will no lead in period, but patients must discontinue BRAF therapy at least 2 weeks or 5 half-lives prior to starting combination therapy on trial (whichever is shorter). Patients with prior disease progression on a BRAF inhibitor will receive continuous dosing of vemurafenib and BKM120 starting on cycle 1, day 1 (See *Figure 5*, Study design). Cycle 1 (28 days) will be defined as the DLT period.

Part A & B

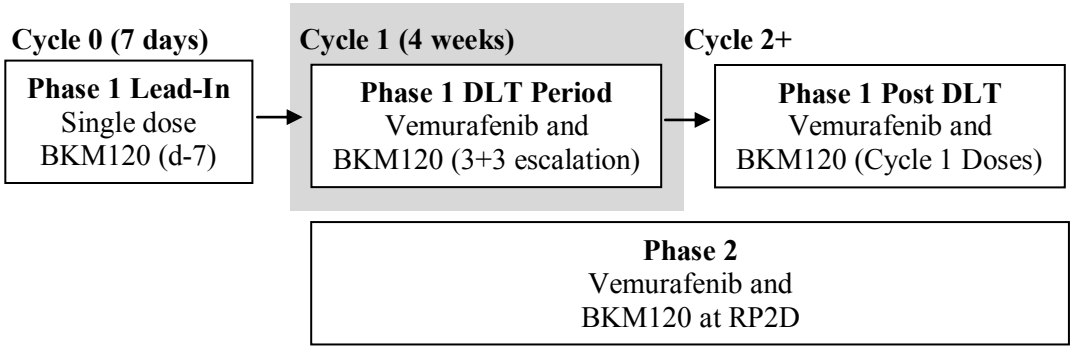
During the phase 1 portion of the study, vemurafenib and BKM120 doses will be escalated using a standard 3+3 dose escalation scheme with the goal of identifying the recommended phase 2 dose (RP2D). Phase 1 dose levels are described in *Table 5* and details regarding dose escalation and identifying the RP2D are given in section 3.3.2.1.

Phase 2

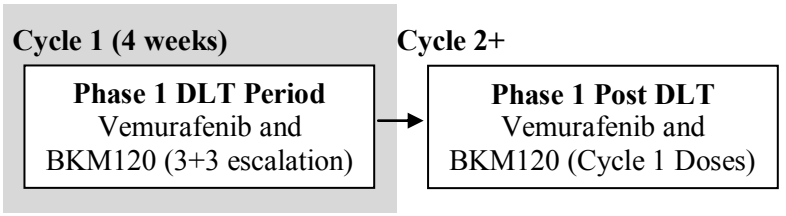
In the phase 2 portion of the study, patients will receive continuous dosing of vemurafenib and BKM120 starting on Cycle 1, Day 1 at RP2D.

Figure 5. Study design

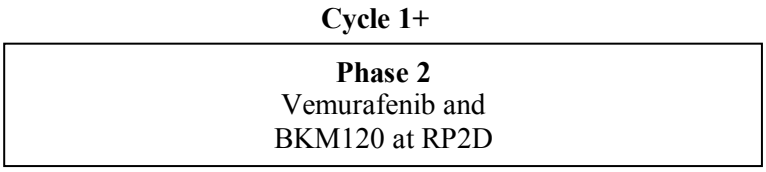
Phase 1-Part A



Phase 1 – Part B



Phase 2



3.2 Study population

3.2.1 Patient population

All patients enrolled willhave metastatic or locally advanced, unresectable $BRAF^{V600E}$ or $BRAF^{V600K}$ mutant melanoma. The study will enroll an estimated total of 61 patients based on an estimate of 27patients in the phase 1 portion of the study and 37 in the phase 2 portion including 6 patients in the phase 1 MTD cohort.

3.2.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations assuring that all inclusion and exclusion criteria have been satisfied must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and

required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. Patients eligible for enrollment in the treatment phase of this study **must meet all** of the following criteria:

Inclusion criteria

1. Histologically or cytologically confirmed diagnosis of unresectable stage III and stage IV melanoma
2. $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive
3. Age ≥ 18 years
4. ECOG performance status ≤ 2
5. Patients must have at least one site of measurable disease [if applicable] (per RECIST for solid tumors or the appropriate disease classification/criteria for the target population)
6. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 109/L, Platelets ≥ 100 x 109/L, Hb>9 g/dL
7. Total calcium (corrected for serum albumin) less than the upper limit of normal (biphosphonate usefor malignant hypercalcemia control is not allowed)
8. Magnesium ≥ the lower limit of normal
9. Potassium within normal limits for the institution
10. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than the upper limit of normal for the institution (or ≤ 3.0 x upper limit of normal (ULN) if liver metastases are present)
11. Serum bilirubin less than the upper limit of normal for the institution(or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with **well documented** Gilbert Syndrome)
12. Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
13. Serum amylase ≤ ULN
14. Serum lipase ≤ ULN
15. INR ≤ 2
16. Fasting plasma glucose ≤ 120 mg/dL (6.7 mmol/L)
17. Negative serum pregnancy test within 72hours before starting study treatment in women with childbearing potential
18. Phase 1, Part B cohort –

    Patients must have previously tolerated continuous dosing of Vemurafenib(at least 720 mg, bid, or higher) without grade 3 or higher toxicity related to the drug (with the exception of keratoacanthomas or squamous cell carcinoma of the skin, grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 7 days of appropriate supportive therapy, grade 3 diarrhea that resolves to Grade ≤ 1 within 7 days with appropriate supportive therapy, grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days, or grade 3 rash that is not deemed to be clinically intolerable).

Exclusion criteria

1. Patients who have received prior treatment with a PI3K inhibitor or a BRAF inhibitor are excluded.

   BRAF inhibitor exposure:

Phase 1, Part A: Patients who have been previously treated with a BRAF inhibitor are excluded. Prior treatment with sorafenib is permitted.

Phase 1 Part B: Patients are required to have had disease progression on a potent BRAF inhibitor such as vemurafenib, dabrafenib, or LGX-818.

Phase 2: Patient population will be determined once Phase 1 has been completed.

2. Patients with a known hypersensitivity to BKM120 or to its excipients
3. Patients with untreated brain metastases are excluded. However, patients with metastatic CNS tumors may participate in this trial, if the patient is > 4 weeks from therapy completion (incl. radiation and/or surgery) and clinically stable at the time of study entry.
4. Patients with acute or chronic liver, renal disease or pancreatitis
5. Patients with the following mood disorders as judged by the Investigator or a psychiatrist, or as a result of patient"s mood assessment questionnaire (See Appendix 1, *Tables A2 and A3*):
    - Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others)
    - ≥ CTCAE grade 3 anxiety
    - Meets the cut-off score of ≥ 10 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or selects a positive response of "1, 2, or 3" to question number 9 regarding potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)
6. Patients with ≥ CTCAE grade 2diarrhea
7. Patient has active cardiac disease including any of the following:
    - Left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc> 480 msec on screening ECG (using the QTcF formula)
    - Personal or family history of prolonged QT syndrome
    - Angina pectoris that requires the use of anti-anginal medication
    - Ventricular arrhythmias except for benign premature ventricular contractions
    - Supraventricular and nodal arrythmias requiring a pacemaker or not controlled with medication
    - Conduction abnormality requiring a pacemaker
    - Valvular disease with document compromise in cardiac function
    - Symptomatic pericarditis
8. Patient has a history of cardiac dysfunction including any of the following:
    - Myocardial infarction within the last 6 months, documents by persistent elevated cardiac enzymes or persistentregional wall abnormalities on assessment of LVEF function
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
9. Patient has poorly controlled diabetes mellitus (HbA_{1c} > 8 %)

10. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
    - Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude pneumonitis or pulmonary infiltrates.
11. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BKM120 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with unresolved diarrhea will be excluded as previously indicated.
12. Patients who have been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued.
13. Patients who are currently receiving treatment with medication with a known risk to prolong the QT interval or inducing Torsades de Pointes and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug. Please refer to *Table A6* or a list of prohibited QT prolonging drugs with risk of Torsades de Pointes.
14. Patients receiving chronic treatment with steroids or another immunosuppressive agent. **Note:** Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intr-articular) are allowed. Patients with previously treated brain metastases, who are on stable low dose corticosteroids treatment (e.g. dexamethasone 2 mg/day, prednisone 10 mg/day) for at least 14 days before start of study treatment are eligible.
15. Patients who have taken herbal medications and certain fruits within 7 days prior to starting study drug. Herbal medications include, but are not limited to St. John‟s Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Fruits include the CYP3A inhibitors Seville oranges, grapefruit, pomelos, or exotic citrus fruits.
16. Patients who are currently treated with drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Please refer to *Table A4* for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).
17. Chemotherapy or targeted anticancer therapy (other than potent BRAF inhibitors)within 5 half-lives of the prior drug orwithin4 weeks (whichever is shorter). Patients may not have exposure to nitrosourea, antibodies or mitomycin-C within 6 weeks prior to starting study drug. Patients must have resolution of treatment related adverse events to baseline or grade 1 before starting the trial.
18. Patients who have received any continuous or intermittent small molecule therapeutics (excluding monoclonal antibodies) ≤ 5 effective half lives prior to starting study drug or who have not recovered from side effects of such therapy
19. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy

20. Patients who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant
21. Women who are pregnant or breast feeding or adults of reproductive potential not employing an effective method of birth control. Double barrier contraceptives must be used through the trial by both sexes. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potentialmust have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment.
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [***for US only***: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
    - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during treatment and for 4 weeks (5 T1/2) after stopping treatment. The highly effective contraception is defined as either:

      1. True 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.

      2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

      3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that patient.

      4. Use of a combination of the following (a+b):

         a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)

         b) Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - Oral contraception, injected or implanted hormonal methods are not allowed as BKM120 potentially decreases the effectiveness of hormonal contraceptives.
    - Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment,and for 4 weeks (5 T1/2) after stopping treatment and for additional 12 weeks (16 weeks in total after study drug discontinuation) and should not father a child in this period.
    - Female partner of male study subject should use highly effective contraception during dosing of any study agent and for 16 weeks after final dose of study therapy
22. Known diagnosis of human immunodeficiency virus (HIV) infection

23. History of another malignancy within 3 years, except cured or curable basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix. Patients with lesions curable by excision must have these lesions excised prior to the initiation of treatment on study.
24. Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

3.3 Treatments

3.3.1 Vemurafenib

Warnings and Precautions

Cutaneous squamous cell carcinomas (cuSCC) occurred in 24% of patients. Perform dermatologic evaluations prior to initiation of therapy and every two months while on therapy. Manage with excision and continue treatment without dose adjustment.

Serious hypersensitivity reactions, including anaphylaxis, have been reported during and upon re-initiation of treatment. Discontinue ZELBORAF in patients who experience severe hypersensitivity reactions.

Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported. Discontinue treatment in patients who experience severe dermatologic reactions.

QT prolongation has been reported. Monitor ECG and electrolytes before treatment and after dose modification. Monitor ECGs at day 15, monthly during the first 3 months of treatment, every 3 months thereafter, or more often as clinically indicated. If the QTc exceeds 500 ms, temporarily interrupt ZELBORAF, correct electrolyte abnormalities, and control for cardiac risk factors for QT prolongation.

Liver laboratory abnormalities may occur. Monitor liver enzymes and bilirubin before initiation of treatment and monthly during treatment, or as clinically indicated.

Photosensitivity has been reported. Advise patients to avoid sun exposure while taking ZELBORAF.

Serious ophthalmologic reactions, including uveitis, iritis and retinal vein occlusion, have been reported. Monitor patients routinely for ophthalmologic reactions.

New primary malignant melanomas have been reported. Manage with excision, and continue treatment without dose modification. Perform dermatologic monitoring as outlined above.

Pregnancy: May cause fetal harm. Advise women of potential risk to the fetus.

BRAFV600E testing – confirmation of BRAFV600E mutation using an FDA-approved test is required for selection of patients appropriate for ZELBORAF therapy. The efficacy and safety of ZELBORAF have not been studied in patients with wild-type BRAF melanoma.

Adverse Reactions

Most common adverse reactions (≥ 30%) are arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus and skin papilloma.

Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

3.3.2 BKM120

Table 4.Serious Adverse Events with a suspected causality

MedDRA System Organ Class	Preferred Term
Blood and lymphatic system disorders	Anaemia, Lymphopenia, Thrombocytopenia
Cardiac disorders	Cardio-respiratory arrest (life-threatening)
Eye disorders	Cataract
Gastrointestinal disorders	Abdominal pain, Colitis, Colitis ulcerative, Constipation, Diarrhoea, Erosive oesophagitis, Mouth ulceration, Nausea, Stomatitis, Vomiting
General disorders and administration site conditions	Asthenia, Fatigue, Mucosal inflammation, Pyrexia
Hepatobilary disorders	Hepatic function abnormal
Immune system disorders	Hypersensitivity
Infections and infestations	Infection, Lower respiratory tract infection*, Pneumonia, Pneumonia bacterial (fatal), Sepsis
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood creatine phosphokinase increased, Transaminases increased
Metabolism and nutrition disorders	Dehydration, Decreased appetite (life-threatening), Diabetic keto-acidosis* (life-threatening), Hyperglycemia* (life-threatening), Hypercreatininemia*, Hyperglycemia, Hyponatraemia, Hypokalaemia (life-threatening)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Neoplasm malignant, Neoplasm progression
Nervous system disorders	Altered state of consciousness*, Cerebral ischemia* (life threatening), Cognitive disorder*, Encephalopathy, Epilepsy , Leukoencephalopathy
Psychiatric disorders	Affective disorder, Anxiety, Confusional state, Depression, Delirium*, Mental status changes, Mood altered, Personality change,
Renal and urinary disorders	Renal failure acute
Respiratory, thoracic and mediastinal disorders	Bronchospasm (life-threatening), Dyspnoea, Interstitial lung disease (fatal), Pneumonitis (fatal)
Skin and subcutaneous tissue disorders	Drug rash with eosinophilia and systemic symptoms (DRESS), Rash, Rash maculo-papular, Photosensitivity reaction

* The late breaking information received after data cut-off date 22 Sep 2011.

Complete and updated adverse event information is available in the Investigational Drug Brochure.

3.3.3 Vemurafenib and BKM120 Administration

Vemurafenibwill be administered on a continuous twice daily dosing schedule and BKM120 will be administered on a continuous once daily dosing schedule. Patients should take the daily dose of BKM120 and vemurafenib in the morning. Patients must fast for at least 2 hours after a light meal before taking daily morning dose of BKM120 and vemurafenib. Vemurafenib and BKM120 should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the capsules as a whole and not chew or crush them. Patients should continue to fast for 2 hours after the administration of each BKM120 dose. Patients should take the second dose of vemurafenib in the evening 2 hours after dinner (evening meal).

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted as an adverse event. In addition, on the days of full pharmacokinetic sampling, the exact time of any episodes of vomiting within the first 4 hours post-dosing on that day and within the first 4 hours following the previous day‟s dosing must be noted whenever possible.

If the patient forgets to take her/his BKM120 dose before 6:00 PM, then the dose should be withheld that day and BKM120 should be restarted the following day. Vemurafenib should be taken twice daily. If a patient forgets to take a dose and it is <6 hours before the next schedule dose, the missed dose should be omitted and vemurafenib should be restarted at the next scheduled dose.

Patients must avoid consumption of St. John‟s Wort, Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, pomelos and exotic citrus fruits from 7 days prior to the first dose of study medication and during the entire study treatment period due to potential CYP3A4 interaction with the study medication. Patients must avoid concomitant intake of strong and moderate CYP3A4/5 inhibitors and inducers. Orange juice is allowed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. If a patient requires a vemurafenib or BKM120 dose delay of > 21 days from the previous dose, the patient must be discontinued from treatment completely and will only require a 28 day follow up visit for study completion.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

3.3.4 Treatment dosing and schedule

3.3.4.1 Phase 1 dosing and dose escalation

During the phase 1 portion, cohorts of patients will be enrolled according to a standard 3 + 3 dose escalation scheme.

Part A

To establish a baseline pharmacokinetic profile for BKM120, phase 1 patients will receive a single dose of BKM120 7 days prior to the initiation of continuous therapy (cycle 0, day -7). PK sampling is described in section 3.4.6. Starting on cycle 1, day 1, patients will receive continuous therapy with vemurafenib and BKM120 during the DLT period (cycle 1 day 1 through cycle 1 day 28) unless dose limiting toxicities occur.Doses will be escalated (see *Table*

5) once the patients receiving the highest current dose have been observed for at least 4 weeks of combination therapy and if DLTs (see *Table 6*) have not been reported in any of 3 patients in a dose level cohort. If 1 of 3 patients experiences a DLT, the cohort will be expanded to six patients and doses will be escalated if no more than 1 of 6 patients in the expanded cohort experiences a DLT. If 2 or more patients in a dose level cohort experience a DLT, then the dose level will be defined as the non-tolerated dose (NTD). Any dose reduction required during the DLT period will be considered a DLT.

The maximum tolerated dose (MTD) for *Part A*will be defined as one dose level below the NTD or BKM120 100 mg PO daily with vemurafenib 960 mg PO bid if this level is achieved without meeting the NTD definition.RP2D will be determined based on the MTD, post-DLT period toxicity, and pharmacokinetic data. There will be no intra-patient dose escalation allowed during the study. For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level.

Part B

Patients must not take BRAF therapy for 2 weeks or 5 half-lives of the BRAF inhibitor prior to initiating combination therapy on trial (whichever is shorter). Starting on cycle 1, day 1, patients will receive continuous therapy with vemurafenib and BKM120 during the DLT period (cycle 1 day 1 through cycle 1 day 28) unless dose limiting toxicities occur.PK sampling is described in section 3.4.6. Doses will be escalated (see *Table 5*) once the patients receiving the highest current dose have been observed for at least 4 weeks of combination therapy and if DLTs (see *Table 6*) have not been reported in any of 3 patients in a dose level cohort. If 1 of 3 patients experiences a DLT, the cohort will be expanded to six patients and doses will be escalated if no more than 1 of 6 patients in the expanded cohort experiences a DLT. If 2 or more patients in a dose level cohort experience a DLT, then the dose level will be defined as the non-tolerated dose (NTD).

The maximum tolerated dose (MTD) for *Part B* will be defined as one dose level below the NTD or BKM120 100 mg PO daily with vemurafenib 960 mg PO bid if this level is achieved without meeting the NTD definition. RP2D will be determined based on the MTD, post-DLT period toxicity, and pharmacokinetic data. There will be no intra-patient dose escalation allowed during the study. For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level. If the maximum tolerated dose has been identified and fewer than 15 patients have been enrolled in Phase 1, Part B, additional patients may be enrolled at the MTD or RP2D at the discretion of the principal investigator to a maximum of 15 patients.

Table 5. Phase 1 dose levels

Dose Level	BKM120 Dose	Vemurafenib Dose
-1	60 mg daily	480 mg bid
1	60 mg daily	720 mg bid
2	80 mg daily	720 mg bid
3	100 mg daily	720 mg bid
4	100 mg daily	960 mg bid

Table 6 – Criteria for defining dose-limiting toxicities

TOXICITY	ANY OF THE FOLLOWING CRITERIA
Hematologic [a]	≥ CTCAE grade 3 neutropenia for > 7 consecutive days CTCAE grade 3 thrombocytopenia for > 7 consecutive days CTCAE grade 4 thrombocytopenia Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)
Renal	Serum creatinine ≥ 2.0 x ULN to ≤ 3.0 x ULN for > 7 consecutive days > CTCAE grade 3 serum creatinine
Hepatic [b]	Total bilirubin ≥ 2xULN to ≤ 3.0 x ULN for > 7 consecutive days > CTCAE grade 3 total bilirubin CTCAE grade 3 AST or ALT for > 7 consecutive days CTCAE grade 4 AST or ALT ALT or AST rise to ≥3x ULN in combination with a rise in bilirubin to ≥ 2x ULN
Endocrine	Grade 2 hyperglycemia (confirmed with a repeat FPG within 24 hours) that does not resolve to grade 0 within 14 consecutive days (after initiation of glimepiride, metformin or glibenclamide) ≥ Grade 3 hyperglycemia (confirmed with a repeat FPG within 24 hours)
Metabolic/ Laboratory	CTCAE grade 3 asymptomatic amylase and/or lipase, not reversible to ≤ CTCAE grade 2 for > 7 consecutive days CTCAE grade 4 asymptomatic amylase and/or lipase
Pancreatitis	≥ CTCAE grade 2
Cardiac	Cardiac toxicity ≥ CTCAE grade 3 or cardiac event that is symptomatic or requires medical intervention Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥ CTCAE grade 3
Neurotoxicity	≥ 1 CTCAE grade level increase
Mood alteration	CTCAE grade 2 mood alteration that does not resolve to ≤ grade 1 within 14 days despite medical treatment (for Anxiety only, if worsened from baseline) ≥ CTCAE grade 3 mood alteration
Dermatologic	Any intolerable phototoxicity or skin toxicity (except SCC of the skin amenable to local excision) ≥ CTCAE grade 3 that does not resolve within 7 days with medical management. Any grade 3 or higher skin toxicity associated with superinfection or limiting self-care ADLs. Secondary squamous cell carcinoma of the skin including but not limited to keratoacanthomas amenable to curative excision or other localized curative therapies are NOT classified as DLTs.
Other adverse events	Grade ≥3 non-hematologic, non-hepatic organ toxicity related to drug regimen, EXCLUDING the following: a. Grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 7 days of appropriate supportive therapy b. Grade 3 diarrhea that resolves to Grade ≤ 1 within 7 days with appropriate supportive therapy c. Grade ≥ 3 fatigue that resolves to Grade ≤2 within 7 days d. Grade ≥ 3 hyperuricemia that resolves to Grade ≤ 2 within 7 days e. Grade 3 fever

a ≥ CTCAE grade 3 anemia will not be considered DLT unless judged to be a hemolytic process secondary tostudy drug. ≥ CTCAE grade 3 lymphopenia will not be considered DLT unless clinically significant.

b For any grade 3 or 4 hepatic toxicity that does not resolve within 7 days to ≤ grade 1 (or ≤ grade 2 if liverinfiltration with tumor present), an abdominal CT scan has to be performed to assess if it is related to diseaseprogression.

A single patient is assumed not to tolerate the dose if he/she experiences at least one DLT.

If a lower grade AE leads to a dose interruption of more than 7 doses of BKM120, this AE will be considered as DLT.

If the 2nd occurrence of an initially non-dose limiting toxicity (e.g., grade 3 AST that resolved to ≤ grade 1 within 7 days at 1st occurrence) leads to a dose reduction within 28 days of the first dose of BKM120, thiswill be considered a DLT.

Parts A & B

Toxicity will be assessed using the NCI Common Toxicity Criteria for Adverse Events, version 4.0 unless otherwise specified (e.g., hyperglycemia). A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs< 28 days following Cycle 1 Day 1 of BKM120 and vemurafenib, and meets any of the criteria listed in *Table 6*.

Whenever a patient experiences atoxicity that fulfills the criteria for a DLT (or a potential DLT), treatment will be interrupted (if not otherwise specified) and the toxicity will be followed up as described in *Table 7*. Exceptions are CTCAE grade 2 hyperglycemia, CTCAE grade 2 mood alteration, and squamous cell carcinoma of the skin that is amenable to cure by local excision. Grade 3 skin toxicity (except SCC of the skin amenable to local excision) and grade 3 photosensitivity will only be considered DLTs if they are intolerable and if they do not resolve within 7 days with appropriate medical management. In the case of hyperglycemia and mood alteration, treatment will be continued under appropriate co-medication, and in the case of SCC of the skin, local excision will be performed. The rules for re-initiation and dose modification of BKM120 and vemurafenibtreatment are outlined in *Table 8*.Prior to enrolling patients into a higher dose level, ≥ CTCAE grade 2 adverse events will be reviewed for all patients at the current dose level.

After the 28-day DLT period, dose modifications will be made as outlined in *Table 8*. Treating physicians must notify the PIimmediately of any unexpected ≥ CTCAE grade 3 adverse events or laboratory abnormalities.

3.3.4.2 Follow-up for dose-limiting toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in *Table 7*, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study. All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of BKM120.

Table 7.Follow-up for dose-limiting toxicities

TOXICITY	FOLLOW-UP EVALUATION
Hematology	If ≥ CTCAE grade 3 neutropenia or ≥ CTCAE grade 3 thrombocytopenia havebeen demonstrated, these labsmust be repeated at least twice a weekuntil resolution to ≤ CTCAE grade 1 neutropenia or ≤ CTCAE grade 1thrombocytopenia to allow for initiation of re-treatment, and then at least weeklyuntil either resolution or until stabilization.
Renal	If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must berepeated at least twice a week until resolution to ≤ CTCAE grade 1 to allow forinitiation of re-treatment, and then at least weekly until either resolution or untilstabilization. If [+3] proteinuria, hematuria ≥ CTCAE grade 2 or serum creatinine ≥ 2.0 x ULN has been demonstrated, a 24-hour urine collection for total protein and total creatinine must be repeated at least weekly until either resolution to baseline value or until stabilization. Whenever a measured CrCl is obtained, a serum creatinine should be obtained within ≤ 72 hours of the urine collection.
Hepatic	If total bilirubin ≥ 2 x ULN in combination with≥ CTCAE grade 3 AST/ALT has beendemonstrated, these parameters must be repeated at least twice a week untilresolution to ≤ CTCAE grade 1 (or ≤ grade 2 for AST or ALT, if liver metastasisare present) to allow for initiation of re-treatment, and then at least weekly untileither resolution or until stabilization.
	Patients with total bilirubin > ULN (any duration) should have fractionation ofbilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Metabolic/ Laboratory	If amylase and/or lipase ≥ CTCAE grade 3 (> 2 x ULN) has been demonstrated,these parameters must be assessed once at 2 to 4 days and once again at 7days (± 1 day) and be repeated twice a week until resolution to ≤ CTCAE grade2 to allow for initiation of re-treatment, and then at least weekly until either resolution to ≤ CTCAE grade 1 or until stabilization. A CT scan or other imaging study to assess the pancreas, liver, and gallbladdermust be performed within 1 week of the first occurrence of any ≥ CTCAEgrade 3 of amylase or lipase. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested in addition.
Endocrine	For details of the follow-up and treatment of ≥ grade 2 hyperglycemia refer to the„Guidelines for the treatment of study drug-induced hyperglycemia“ provided insection 3.3.6.2.2.
Cardiac	Patient who experience QTc prolongation should be followed as per *Table 6.*In addition, patients who experience ECG abnormalities indicative of an ischemic cardiac event, ECGs should be repeated at least twice a week until normalization or stabilization of ECG findings. If troponin ≥ CTCAEgrade 3 has been demonstrated, this parameter must be repeated twice a week until resolution to ≤ CTCAE grade 1 to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization
Neurotoxicity	Patients who experience neurotoxicity should be followed as per *Table 6.*
Mood alteration ≥ grade 2 Note: For grade 2 Anxietyonly, if worsened from baseline	For patient who experience ≥ grade 2 mood alteration a psychiatrist must be consulted for diagnosis and determination of most appropriate medical treatment. Patients must be followed twice weekly by patient self-rating mood scale and be seen weekly by the psychiatrist until resolved ≤ grade 1 or baseline (for anxiety). Continue to test weekly by mood scale until resolution to baseline or stabilization. Refer to Section 3.3.5.2.1 for more details.
Non-Laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, stabilization of the toxicity, or study treatment completion.

3.3.4.3 Dose expansion and phase 2 dosing

After the RP2D is identified in Phase I, Part A, the RP2D cohort for BRAF inhibitor naïve patientswill be expanded to a total of 37 patients for the phase 2 portion of the trial. Dose modifications in the phase 2 portion of the trial will be made as outlined in *Table 9*.

3.3.5 Interruption or discontinuation of treatment

For patients who develop dose-limiting adverse events despite maximum supportive care after the DLT period in the phase 1 portion or at any time in the phase 2 portions of the study, dose adjustments are permitted. The criteria for dose adjustments for vemurafenib and BKM120 are described in *Table 8*. Since the study drugs have overlapping toxicities, the doses of both drugs will be reduced sequentially for all toxicities other than hyperglycemia, pneumonitis and anxiety, which are unique to BKM120. The dose levels for drug associated adverse events other than hyperglycemia, pneumonitis, and anxiety are outlined in *Table 9*. Reduction of the dose of BKM120 alone by increments of 20 mg per dose will be made for hyperglycemia, pneumonitis and anxiety with a maximum of 2 dose reductions permitted.

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose levels
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit both drugs until resolved to ≤ Grade 1, and/or: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Febrile neutropenia (ANC < 1.0 x 10^9/L,fever ≥ 38.5°C)	Omit both drugs until resolved, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit both drugs until resolved to ≤ Grade 1, and/or: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 4 (PLT < 25 x 10^9/L)	Omit both drugs until resolved to ≤ Grade 1, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
HEPATIC	
Bilirubin (*for patients with Gilbert	Will be fractionated if elevated

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	*Omit* both drugs until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	*Omit* both drugs until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9* • If resolved in > 7 days discontinue patient from study treatment
Grade 4 (> 10.0 x ULN)	*Omit* both drugs and discontinue patient from study

AST or ALT	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level with LFTs monitored as per protocol
Grade 2 (> 3.0 - 5.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ grade 1, then • If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	*Omit* both drugs until resolved to ≤ Grade 1 , then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	*Omit* both drugs until resolved to ≤ Grade 1, (then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue study treatment permanently.

* LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT.

Monitoring (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT.

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
ENDOCRINE/METABOLIC	
Fasting Plasma Glucose (FPG)	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	Maintain dose level, check FPG every week • initiate or intensify medication with appropriate anti-diabetic treatment. as per investigator‟s discretion • instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study • check FPG weekly for 8 weeks, then continue checking every 2 weeks
Grade 2 (>160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	First Occurrence: Maintain dose, re-check FPG within 24 hours, if no worse than Grade 2*: • maintain dose level • initiate or intensify medication with appropriate anti-diabetic treatment. • instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study If FPG does not resolve to ≤ Grade 1 within 14 days after initiation/intensifying anti-diabetic treatment: omit BKM120 • monitor FPG at least weekly until FPG resolves to ≤ Grade 1 • then re-start BKM120 and ↓ 1 BKM120 dose level (-20 mg) • continue with anti-diabetic treatment • check FPG weekly for 8 weeks, then continue checking every 2 weeks * if grade “worsens” then follow specific grade recommendations
Grade 2 (>160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	Second Occurrence: maintain dose, re-check FPG within 24 hours, if no worse than Grade 2*: • omit BKM120 • initiate or intensify medication with appropriate anti-diabetic treatment • monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 • then re-start BKM120 and ↓ 1 dose level (-20 mg) • continue with anti-diabetic treatment

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
	• check FPG weekly for 8 weeks, then continue checking every 2 weeks * if grade "worsens" then follow specific grade recommendations
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	First Occurrence: *Omit* BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours, if no worse than Grade 3*: • monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 • stop or reduce insulin medication • then re-start BKM120 and ↓ 1 BKM120 dose level(-20 mg) • continue with anti-diabetic treatment as appropriate • instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study • check FPG weekly for 8 weeks, then continue checking every 2 weeks Second Occurrence: Same process as for first occurance, however at the second re-initiation BKM120 may be dose-reduced a second time. * if grade "worsens" then follow specific grade recommendations
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	Immediately omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours, if confirmed Grade 4: • Discontinue patient from BKM120 Patient may continue vemurafenib. • instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study • check FPG weekly for 8 weeks, then continue checking every 2 weeks
CARDIAC	
Cardiac – Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 50 – 40%; or 10-20% drop from baseline	Maintain dose level
Symptomatic, responsive to intervention,	*Omit* both drugs until resolved to ≤ Grade 1, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
ejection fraction 39 – 20% or > 20% drop from baseline	LVEF measurement to be repeated, if not resolved to ≤ Grade 1 within 3 weeks, permanently discontinue patient from study
Refractory or poorly controlled, ejection fraction < 20%	*Omit* both drugs and discontinue patient from study
Cardiac – QTc prolongation	
QTcF> 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	First Occurrence: • *Omit* both drugs • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTcF of > 500 ms • If QTcF remains > 500 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. • Once QTcF prolongation has resolved, BKM120 may be restarted at a one lower dose level Second Occurrence: • discontinue patient from vemurafenib/BKM120
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	*Omit* both drugs until resolved to ≤ Grade 1, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 4	Discontinue patient from study
OTHER	
Mood alteration	
* See *Table A1-3* for toxicity grading of mood questionnaires. Questionnaire scores should be considered when assigning the AE Grade but psychiatric consult, if required, may determine the grade	
Grade 1 (or Grade 2 anxiety if present at baseline)	Maintain dose level Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Grade 2 (for Anxiety only, if worsened from baseline)	Institute appropriate co-medication under the guidance of the psychiatrist. Maintain dose level. • If the condition does not resolve to ≤ Grade 1 within 14 days despite medical treatment; then ↓ 1 BKM120 dose level (-20 mg, continue to co-medicate)

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
	Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 BKM120 dose level (-20 mg, co-medicate) Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Grade 4	Omit BKM120 dose and discontinue BKM120. Patient may continue to receive vemurafenib. Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Rash	
Grade 1	Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 2	Maintain dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 3	Hold both drugs for any grade 3 rash that is intolerable, associated with superinfection, or limiting self-care ADLs until resolved to CTCAE Grade ≤ 2, then: • If resolved in ≤ 7 days, ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9* • If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue patient from BKM120
Grade 4	*Omit* both drugs and discontinue patient from study
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 4	Omit dose and discontinue patient from BKM120. Patient may continue to receive vemurafenib
Other non-hematological adverse events	
Grade 1 or 2	Maintain dose level
Grade 2 (pancreatitis)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level

Table 8. Criteria for interruption and re-initiation of vemurafenib and BKM120 treatment

Recommended Dose Modifications for vemurafenib and BKM120

*Worst toxicity (CTCAE Grade)***	*Recommended Dose Modifications*
	• If resolved in > 7 days, ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9*
Grade 3	*Omit* both drugs until resolved to ≤ Grade 1, then ↓vemurafenib/BKM120 1 dose level as outlined in *Table 9.* *No treatment changes are required for keratoacanthomas or other squamous cell carcinoma skin lesions that are curable by local excision.* *For grade 3 asymptomatic lipase and/or lipase, omit both drugs until resolved to ≤ Grade 1, then ↓ vemurafenib/BKM120 1 dose level as outlined in Table 9 if not reversible to ≤ grade 2 within 7 consecutive days.*
Grade 4	*Omit* both drugs and discontinue patient from study Note: Omit dose for ≥ Grade 3 nausea, vomiting or diarrhea only if the nausea, vomiting or diarrhea cannot be controlled with optimal antiemetic or antidiarrheal regimen. *No treatment changes are required for keratoacanthomas or other squamous cell carcinoma skin lesions that are curable by local excision.*
Pneumonitis	See *Table 11*

** Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 9. Vemurafenib-BKM120 dose reductions for all toxicities other than hyperglycemia and anxiety

Dose Level at which toxicity requiring dose reduction occured	Reduce to:
-1	Vemurafenib 240 mg bid with BKM120 60 mg daily
1	Table 5, dose level -1
2	Table 5, dose level 1
3	Table 5, dose level 2
4	Table 5, dose level 3

Dose levels are outlined in Tables 5

3.3.6 Monitoring vemurafenib suspected toxicities

3.3.6.1 Known undesirable side effects of vemurafenib

Common grade 2 or higher drug-related adverse events of vemurafenib in phase 1 testing included rash, photosensitivity, pruritis, palmar-plantar dysesthesias, squamous cell carcinomas of the skin/keratoacanthomas, fatigue, nausea, and arthralgias[4]. Only four patients had grade 4 adverse events potentially related to vemurafenib: two had GGT elevations, one had fatigue, and one had pancytopenia. In general, pain complaints should be managed with acetaminophen and mild narcotic pain medications, and nausea should be managed with oral prochlorperazine or ondansetron as needed. Dose adjustments may be required for persistent symptoms or laboratory abnormalities despite optimal symptomatic support (see *Table 8*).

3.3.6.1.1 Dermatologic events

15% of patients in the phase 1 dose-escalation cohort and 31% in the dose expansion cohort developed treatment-associated squamous-cell carcinomas and nearly all of these were histologically consistent with keratoacanthomas[4]. The median time to appearance of these lesions was 8 weeks. All were treated with local excision and no treatment modifications were required. No other squamous cell malignancies have been reported with vemurafenib. Patients on the current study will be assessed by the study dermatologist prior to the initiation of treatment on vemurafenib and all lesions that are suspicious for malignancy should be excised. During pre-treatment and follow-up visits, pre-malignant lesions may be treated with excision, cyroablation, or other standard-of-care techniques at the discretion of the dermatologist. Follow-up dermatologic evaluation will be scheduled prior to the initiation of BKM120 and then every eightweeks (+/- 3 days) and earlier evaluations should be scheduled if any suspicious lesions emerge between these scheduled visits.

Rash is a common adverse event associated with vemurafenib and symptomatic treatments including antihistamines, antibiotics such as tetracyclines, and topical corticosteroids may be used at the discretion of the treating clinician. Short-term oral corticosteroids (< 10 days) may be used with the consent of the Principal Investigator, and patient receiving both oral corticosteroids and BKM120 should be instructed regarding home blood glucose monitoring.

Monitoring of BKM120 suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in *Table 7*, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. After the DLT evaluation period, if a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study. If the patient requires more than 2 dose reductions, the patient should be discontinued from the study.

3.3.6.2 Known Undesirable Side Effects of BKM120

3.3.6.2.1 Neuropsychiatric events

This adverse event emerged as a side effect related to BKM120. Studies conducted *in vitro* and *in vivo* hypothesize that PI3K/Akt and Akt/GSK3 signaling pathways are associated and modulated by changes of monoamine transmitters (dopamine and serotonin 5-HT)[33-35]. BKM120 showed penetration in brain tissue in animal models. In preclinical safety studies with BKM120 neither an evidence of impaired neuronal function nor any morphologic changes of the central nervous system were detected. Clinically, as of 10/25/10, 29 out of 69 patients (42%), treated with BKM120 as a single agent (in trial BKM120X2101), experienced mood alterations such as anxiety, agitation, crying episodes, depression and behavioral changes with aggressive components. Grade 3 events (severe mood alteration interfering with active daily life activities) were reported in 5 patients (7%). No grade 4 events have been observed thus far. All the events have been observed at a BKM120 dose of 80 mg/day or higher with onset occurring within 28 days after treatment initiation. Symptoms improved when treatment was interrupted. Patients with a medical history of depression or anxiety experienced the most severe episodes, however if concomitantly treated with antidepressants, did not develop psychiatric symptoms during study drug administration. In some patients the causal relationship with BKM120 was not clearly established because the patients may have been influenced by negative events related to their close family or friends. Benzodiazepine introduction and BKM120 dose reduction well controlled the mood in patients who continued on treatment.

Due to the frequency and peculiarity of this side effect, a scientific advice was sought through an advisory board held in November 2009. Some corrective measures identified by the advisory board included additional exclusion criteria and new procedures for mood alteration monitoring and follow-up. Patient self-rating mood questionnaires for anxiety (GAD-7) and depression (PHQ-9) were implemented in the study BKM120X2101 in January 2010. As shown in *Table 10* these measures have led to a reduction in the number and the severity of the observed events of mood disorder as well as the number of discontinuations due to this adverse event.

Table 10.Mood disorders adverse events reported in trial CBKM120X2101 (As of 10/25/10)

Mood disorders	Before Jan 2010 (N=42)	After Jan 2010 (N=27)
All grades	26 (62%)	10 (37%)
Grade 3	3 (7%)	2 (7%)
Discontinuations	2 (5%)	None

In order to lower the risk of experiencing significant mood alterations within the proposed study, cancer patients with an active or history of major depressive episode, bipolar disorder, obsessive-compulsive disorder, schizophrenia, a history of suicide attempt or ideation, or homicide/homicidal ideation as judged by the investigator and/or based on recent psychiatric assessment will not qualify for study participation. For patients with corresponding symptoms CTCAE Grade ≥ 2, thestudy psychiatrist will be consulted for diagnosis and determination of most appropriate medical treatment Medical treatment with mood stabilizers (2nd generation antipsychotics) such as olanzapine and quetiapine may be applied as per investigator"s discretion and following consultation of the study psychiatrist.

The study psychiatrist at UCSF is:

Laura Dunn, MD
Associate Professor in Residence
UCSF Department of Psychiatry
Box 0984 - F, 401 Parnassus Ave, LangPorter LP254
University of California, San Francisco
San Francisco, CA. 94143 - 0984
Phone: (415) 476-7518

Management of mood alteration

Patient self-rating mood questionnaires GAD-7 (anxiety, Appendix, *Table A2*), and PHQ-9 (depression, Appendix, *Table A3*) will be used:

- to support assessment of eligibility at Screening
- to monitor for newly occurring or worsening mood alterations during the study

The mood alteration grading system is outlined in the appendix and in *Table A1*.

At Screening, a patient as judged by the investigator or who meets the cut-off score of ≥ 10 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, will be excluded from the study unless overruled by the psychiatric assessment.

During the study, for patients who meet the cut-off score of ≥ 10 (≥ CTCAE grade 2 moodalteration) in either questionnaire, a psychiatrist will be consulted for diagnosis and determination ofmost appropriate medical treatment. For anxiety, this applies only if status has worsened frombaseline. Patients who experience ≥ grade 2 mood alteration will be followed weekly by

patient self-rating mood scale and will be seen weekly by the psychiatrist until resolved ≤grade 1 or baseline (for anxiety). Questionnaire responses will be checked by the psychiatristat the weekly visits (until resolution to Grade 1) or baseline (for anxiety).

3.3.6.2.2 Hyperglycemia

In preclinical studies, insulin/glucose homeostasis was impacted in various species (mice, rats, dogs), as expected from the mode of action of BKM120. In both rats and dogs, at the doses used in the 4-week studies, these effects were minimal. However, in mice treated at high doses (30 or 60 mg/kg/day) a clear induction of insulin resistance/insensitivity was observed. There wasno clear influence of the dose or the time point of testing. Histopathologically, pancreas and liver showed changes were noted which are in concordance with this activity.

Grade 4 Hyperglycemia was also observed in a Phase 1a study of BKM120 in patients with solid tumors (CBKM120X2101). Therefore, no patients with uncontrolled diabetes mellitus will be enrolled in this study. In all patients, fasting plasma glucose will obtained at screening and will be monitored throughout the trial. For the treatment of glucose disturbances occurring under BKM120 treatment investigators are advised to adhere to the protocol guidelines outlined in *Table 8* and in the following section.

Management of Hyperglycemia

In addition to the dose modification and hyperglycemia treatment guidelines in *Table 8*:

- Insulin regimen should be initiated according to institutional standard of care or the Treat-To-Target Algorithm for Lantus®[36].
- For any hyperglycemia ≥ grade 1, the patient should continue to follow dietary guidelinesprovided by the American Diabetes Association (American Diabetes Association 2004).
- Patients with ≥ grade 3 hyperglycemia who do not have indications for hospitalization should be advised to initiate home glucose monitoring with twice daily finger sticks until hyperglycemia resolves to ≤ grade 1.
- For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated in that patient during future treatment cycles with BKM120.
- For each patient, a maximum of 2 dose reductions will be allowed after which the patient should be discontinued from the study. In addition, a patient must discontinue treatment with BKM120, if after treatment is resumed at a lower dose, hyperglycemia recurs at a worse severity.
- Based upon the results of preliminary clinical data and actual laboratory values (e.g., glucose, insulin) generated, the treatment recommendations for study drug induced hyperglycemia may be modified as needed.

3.3.6.2.3 Cardiac events

Cardiac safety studies, conducted in vitro and in vivo, did not indicate a prominentelectrophysiological risk. The only effect considered relevant was a trend towards an increasein systolic and diastolic blood pressure, observed in two dog telemetry studies.As a precaution in the first-in man study with BKM120 no patients with a severe orunstablecardiac disease or cardiac disease requiring continuous treatment, and no patients withuncontrolled hypertension will be enrolled in early clinical studies. In addition, all patientswill be assessed for cardiac diseases before start of treatment, while all patients enrolled in thetrial will undergo regular cardiac monitoring throughout the conduct of the trial. EKGs will be reviewed by the Principal Investigator and recorded in the OnCore clinical trial records system. For thetreatment of acute cardiac events occurring under BKM120 treatment investigators areadvised to adhere to the protocol guidelines. Vital signs, including pulse rate and bloodpressure, will closely be followed during the early clinical studies.

Management of Cardiac events

A 12-lead electrocardiogram (ECG), and an echocardiogram will be performed at the Screening Visit to assess eligibility. Repeat ECGs will be performed (+/- 2 days) on cycle 1 day 15, on cycle 2, 3, and 4 day 1, and every 3 months thereafter in accordance with the manufacturer‟s standard-of-care recommendations for vemurafenib. An ECHO/MUGA will be repeated at Cycle 4 and then every 4th cycle thereafter.

Management of Pneumonitis

Pneumonitis is a known side effect of rapamycin analogues. Based on the literature, the class of PI3K inhibitors has not previously been associated with the development of Pneumonitis. Clinically significant Pneumonitis is typically accompanied by non-specific symptoms including dyspnea, nonproductive cough, fatigue, and fever. Diagnosis is generally suspected in individuals who develop these symptoms or in asymptomatic individuals in whom a routine chest CT scan reveals a new ground glass or alveolar infiltrate.

In ongoing clinical trials with BKM120 in the single agent setting two cases of pneumonitis occurred. In the study BKM120X2101 one patient experienced grade 2 pneumonitis eight weeks after the first dose of BKM120 at 100mg which resolved in 7 days after antibiotic therapy and discontinuation of the study treatment due to fatigue. In the Japanese study BKM120X1101 one case of pneumonitis occurred in a patientone month after the start of study medication with BKM120 at a dose of 100 mg daily. The patient experienced pneumonitis with concomitant progression of underlying malignancy including the progression of existing and the appearance of new lesions in combination with increasing pleural effusion (please see current IB for more details). The patient ultimately died from this episode.

All patients participating in clinical trials administering BKM120 will be routinely asked about the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function test should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed pneumonitis. In case of a documented pneumonitis, guidelines (including dose modifications) for

management are described in*Table 11*. Consultation with a pulmonologist is highly recommended for any pneumonitis case identified during the study.

Table 11Management of pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	BKM120 Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of BKM120 dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce BKM120 dose by 1 dose level (see Table 9) until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with BKM120 until recovery to ≤ Grade 1. May restart study treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with BKM120.

Management of Liver Toxicities

Monitoring Cycle 1 and 2: **every other week** (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT/ bilirubin* values.

Monitoring Cycle 3 and more:**monthly** or more frequently if clinically indicated. In case of any occurrence of ALT/ AST/ bilirubin* increase ≥ **grade 2** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ grade 1.**

In case of any occurrence of ALT/ AST/ bilirubin* increase **≥grade 3** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ grade 1**; thereafter the monitoring should be continued **every other week** or more frequently if clinically indicated **until the end of treatment with study medication.**

Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated **until resolved to ≤ grade 1 or stabilization** (no CTCAE grade change over 4 weeks).

Study discontinuation

All interruptions or changes to study drug administration must be recorded.

The investigator or his staff will document whether each patient completes, and the reason for the cessation of treatment on study or the cessation of data collection will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

3.3.7 Concomitant therapy

All medications (excluding prior chemotherapy and biologic, immunologic or radiation therapy) taken within 4 weeks prior to the administration of vemurafenib and BKM120 and all concomitant therapy administration during the study with reasons for therapy should be recorded. All prior chemotherapy; biologic, immunologic or radiation therapy; and surgery within 4 weeks prior to the administration of study drug, will be recorded.

Patients on chronic medications that can be given concomitantly with vemurafenib and BKM120 should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions described in section 3.3.6.1.

3.3.7.1 Drugs that are prohibited

- Other investigational therapies must not be used while the patient is on the study.
- Systemic anticancer therapy (chemotherapy or biologic therapy) other than the study treatments must not be given to patients while the patient is on the study. If such agents are required for a patient then the patient must be discontinued from the study.
- In *vitro* metabolism studies suggest that oxidative metabolism of BKM120 is predominantly mediated by CYP3A4 (fm>0.9), with only minor contributions of CYP1A1. As BKM120 is a sensitive CYP3A4 substrate, co-administration of BKM120 with strong and moderate CYP3A4 inhibitors and CYP3A4 inducers is prohibited. Refer to *Table A4* for a list of prohibited drugs. Please note this list may not be comprehensive.
- Based on in vitro studies, co-administration of BKM120 with CYP3A4 inducers is predicted to decrease the systemic exposure to BKM120, thereby increasing the risk of exposing the patient to subtherapeutic drug levels. Refer to *Table A4* for a list of prohibited CYP3A inducers. Please note that this list may not be comprehensive.
- Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-derivative anticoagulants are not permitted.
- If a patient requires the concomitant use of any medication included in *Table A4* entitled "List of Prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a risk of causing Torsades des de Pointes), study treatment administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to St. John‟s Wort, Kava, ephedra (ma huang), ginkobiloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
- Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective in this study.

3.3.7.2 Drugs to be used with caution

Preliminary in vitro metabolism studies suggest that BKM120 is a weak, reversible inhibitor CYP3A4/5 (Ki=13.6 μM, [I]/Ki= 0.4 where [I] is the average C_{max} at steady-state following 100 mg daily dose) and a weak reversible inhibitor of CYP2C8/2C9/2C19 (IC_{50}=34 μM, [I]/IC_{50}=0.15). Note: that with the data available, we are not able to confirm whether such interactions will occur in patients. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Patients receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate. Please refer to *Table A5* for a list of CYP450 substrates and carefully consider their co-administration with BKM120. Particularly, caution is advised when BKM120 is co-administered with:

- Drugs which are substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index.

- Oral anti-diabetics which are metabolized by CYP2C8 or CYP2C9 can possibly result in hypoglycemia. Patients who develop diabetes mellitus during the study should be treated according to the American Diabetes Association guidance. It is recommended that treatment start with metformin. Note that the use of troglitazone and pioglitazone is prohibited due to possible induction of CPY3A4 which can be expected to decrease BKM120 exposure to subtherapeutic levels.
- Concomitant treatment with corticosteroids and BKM120 should be avoided, whenever possible, during this study.
- If a patient, after study enrollment, requires the concomitant use of any medication which may cause QT prolongation and/or torsade de pointes then the investigators, at their discretion, may co-administer such medications. Patients receiving such medications must be monitored. Refer to *Tables A6 and A7* for a list of medications which may prolong QT.
- Please refer to *Table A5* for a list of CYP450 substrates and carefully consider their co-administration with BKM120.
- A short duration (< 2 weeks) of systemic corticosteroids is allowed (e.g. for chronic obstructive pulmonary disease, or as an anti-emetic). Chronic dosing of corticosteroids is known to induce CYP3A enzymes, thereby increasing the risk or reducing BKM120 overall exposure to sub-therapeutic levels.

3.4 Visit schedule and assessments

3.4.1 Visit schedule

Table 11a. Evaluation and visit schedule for phase 1, part Aof the study

+ / - 1 day window is allowed for cycle 1 procedures. + / - 3 days window is allowed for all subsequent cycles unless otherwise noted.

Assessment	Screening[13]	Cycle 0		Cycle 1				Cycle 2		Cycle 3	Future Cycles (even)	Future Cycles (odd)	Progression
Study Day/Visit Day		-7	-4	1	8	15	22[14]	1	15	1	1	1	
Informed consent	X												
Background information	X												
Serum Pregnancy Test (WOCBP)	X												
Physical Exam	X			X	X	X	X	X	X	X	X	X	X
Dermatology Exam	X									X		X	X
Vitals	X			X	X	X	X	X	X	X	X	X	X
ECOG PS	X			X	X	X	X	X	X	X	X	X	X
Neuropsychiatric Assessment[1]	X			X		X		X	X	X	X	X	
Adverse Event Assessment	X			X	X	X	X	X	X	X	X	X	
Hematology[2]	X			X	X	X	X	X	X	X	X	X	X
HbA_{1c} and C-peptide[3]	X							X			(X)	(X)	
Chemistry[4]	X	X		X	X	X	X	X	X	X	X	X	X
Coagulation[5]	X							X			X		X
Fasting Blood Glucose[6]	X			X		X		X	X	X	X	X	
Urinalysis[7]	X												X
Radiographic Tumor Assessment[8]	X									X		X	X
RECIST reading	X									X		X	
Tumor Biopsy[9]	X					X							X
BRAF Testing	X												
MUGA/Echo[10]	X										(X)		
ECG[11]	X					X		X		X	(X)	(X)	X
PK[12]		X	X	X		X		X		X	(X)		

1 Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study.

2 Hematology - WBC plus differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts, hemoglobin and platelets.

3 HbA_{1c} and C-peptide will be measured at screening and on Day 1 of every third treatment cycle starting with Cycle 2 Day 1 and at EOT.

4 Biochemistry - K+, Na+, Ca++, Mg++, LDH, ALT, AST, total bilirubin (direct and indirect), creatinine, amylase, GGT, lipase, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, phosphorus, uric acid, total cholesterol, HDL, LDL, triglycerides, glucose, urea or BUN, albumin, and total protein are required at baseline and at end of treatment. Subsequent assessments always include K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, alkaline phosphatase, bicarbonate, phosphorus, glucose, urea or BUN, albumin, and total protein BUT, lipase, total cholesterol, HDL, LDL, triglycerides should be obtained on the first day of odd numbered cycles only. C1D-7 assessments may be performed up to 72 hours prior to the scheduled visit.

5 Coagulation - PT or INR, PTT. Patient entering the study while receiving anti-coagulation therapy or those who have the initiation of an anti-coagulation therapy should have their coagulation test performed on a weekly basis.

6 Patients must be fasting overnight for at least 8 hours. Additional measurements may be performed as clinically indicated.

7 Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

8 Screening radiological assessments should be performed within 4 weeks of the first dose. Radiological tumor assessment should be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks of combination therapy (first restaging at the end of week 8), until progression of disease or end of treatment. All assessments should be performed within ±7 days of the scheduled day of assessment. The assessment at the end of treatment visit is only to be performed if the prior assessment occurred ≥ 21 days before.

9 Biopsies will be done at Screening, Cycle 1 Day 15, and within 14 days of any radiographic examination documenting disease progression by RECIST from all patients with visible or palpable disease unless the PI determines thata biopsy would pose an unacceptable risk to the patient.

10 Echo/MUGA will be performed at baseline and every 4 cycles, or more often as clinically indicated.

11 ECG will be performed at baseline and (+/- 2 days) on cycle 1 day 15, on cycle 2, 3, and 4 day 1, and every 3 months thereafter in accordance with the manufacturer"s standard-of-care recommendations for vemurafenib

12 PK analysis will only be performed during the phase 1 portion of the study. See section 3.4.6 for schedule.

13 Laboratory assessments including hematology, blood chemistries, and fasting blood glucose do not need to be repeated prior to the first dose of BKM120 if screening laboratories were performed within 14 days of this date.

14 If toxicity is present at C1D15, C1D22 visit may be done at the discretion of the physician.

Note: A Brain MRI may be performed at screening and/or at any time during the study as clinically indicated

Table 11b. Evaluation and visit schedule for phase 1, part Bof the study

+ / - 1 day window is allowed for cycle 1 procedures. + / - 3 days window is allowed for all subsequent cycles unless otherwise noted.

Assessment	Screening	Cycle 1				Cycle 2		Cycle 3	Future Cycles (even)(odd)		Progression
Study Day/Visit Day		1[13]	8	15	22[14]	1	15	1	1	1	
Informed consent	X										
Background information	X										
Serum Pregnancy Test (WOCBP)	X										
Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Dermatology Exam	X							X		X	X
Vitals	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric Assessment[1]	X	X		X		X	X	X	X	X	
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	
Hematology[2]	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c} and C-peptide[3]	X					X			(X)	(X)	
Chemistry[4]	X	X	X	X	X	X	X	X	X	X	X
Coagulation[5]	X					X			X		X
Fasting Blood Glucose[6]	X	X		X		X	X	X	X	X	
Urinalysis[7]	X										X
Radiographic Tumor Assessment[8]	X							X		X	X
RECIST reading	X							X		X	
Tumor Biopsy[9]	X			X							X
BRAF Testing	X										
MUGA/Echo[10]	X										
ECG[11]	X			X		X		X	(X)	(X)	X
PK[12]		X		X		X		X	(X)		

1 Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study.

2 Hematology - WBC plus differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts, hemoglobin and platelets.

3 HbA_{1c} and C-peptide will be measured at screening and on Day 1 of every third treatment cycle starting with Cycle 2 Day 1 and at EOT.

4 Biochemistry - K+, N_{a+}, Ca++, Mg++, LDH, ALT, AST, total bilirubin (direct and indirect), creatinine, amylase, GGT, lipase, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, phosphorus, uric acid, total cholesterol, HDL, LDL, triglycerides, glucose, urea or BUN, albumin, and total protein are required at baseline and at end of treatment. Subsequent assessments always include K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, alkaline phosphatase, bicarbonate, phosphorus, glucose, urea or BUN, albumin, and total protein BUT, lipase, total cholesterol, HDL, LDL, triglycerides should be obtained on the first day of odd numbered cycles only.

5 Coagulation - PT or INR, PTT. Patient entering the study while receiving anti-coagulation therapy or those who have the initiation of an anti-coagulation therapy should have their coagulation test performed on a weekly basis.

6 Patients must be fasting overnight for at least 8 hours. Additional measurements may be performed as clinically indicated.

7 Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

8 Screening radiological assessments should be performed within 4 weeks of the first dose. Radiological tumor assessment should be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks of combination therapy (first restaging at the end of week 8), until progression of disease or end of treatment. All assessments should be performed within ±7 days of the scheduled day of assessment. The assessment at the end of treatment visit is only to be performed if the prior assessment occurred ≥ 21 days before.

9 Biopsies will be done at Screening, Cycle 1 Day 15, and within 14 days of any radiographic examination documenting disease progression by RECIST from all patients with visible or palpable disease unless the PI determines that a biopsy would pose an unacceptable risk to the patient.

10 Echo/MUGA will be performed at baseline and every 4 cycles, or more often as clinically indicated.

11 ECG will be performed at baseline and (+/- 2 days) on cycle 1 day 15, on cycle 2, 3, and 4 day 1, and every 3 months thereafter in accordance with the manufacturer"s standard-of-care recommendations for vemurafenib

12 PK analysis will only be performed during the phase 1 portion of the study. See section 3.4.6 for schedule.

13 Laboratory assessments including hematology, blood chemistries, and fasting blood glucose do not need to be repeated prior to the first dose of BKM120 if screening laboratories were performed within 72 hours of C1D1.

14 If toxicity is present at C1D15, C1D22 visit may be done at the discretion of the physician.

Note: A Brain MRI may be performed at screening and/or at any time during the study as clinically indicated

Table 11c. Evaluation and visit schedule for phase 2 of the study

+ / - 1 day window is allowed for cycle 1 procedures. + / - 3 days window is allowed for all subsequent cycles.

Assessment	Screening	Cycle 1				Cycle 2		Cycle 3	FutureCycles (even)(odd)		Progression
Study Day/Visit Day		1[12]	8	15	22[13]	1	15	1	1	1	
Informed consent	X										
Background information	X										
Serum Pregnancy Test (WOCBP)	X										
Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Dermatology Exam	X							X		X	X
Vitals	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric Assessment[1]	X	X		X		X	X	X	X	X	
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	
Hematology[2]	X	X	X	X	X	X	X	X	X	X	X
HbA_{1c} and C-peptide[3]	X					X			(X)	(X)	
Chemistry[4]	X	X	X	X	X	X	X	X	X	X	X
Coagulation[5]	X					X			X		X
Fasting Blood Glucose[6]	X	X		X		X	X	X	X	X	
Urinalysis[7]	X										X
Radiographic Tumor Assessment[8]	X							X		X	X
RECIST reading	X							X		X	
Tumor Biopsy[9]	X			X							X
BRAF Testing	X										
MUGA/Echo[10]	X								(X)		
ECG[11]	X			X		X		X	(X)	(X)	X

1 Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study.

2 Hematology - WBC plus differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts, hemoglobin and platelets.

3 HbA_{1c} and C-peptide will be measured at screening and on Day 1 of every third treatment cycle starting with Cycle 2 Day 1 and at EOT.

4 Biochemistry - K+, Na+, Ca++, Mg++, LDH, ALT, AST, total bilirubin (direct and indirect), creatinine, amylase, GGT, lipase, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, phosphorus, uric acid, total cholesterol, HDL, LDL, triglycerides, glucose, urea or BUN, albumin, and total protein are required at baseline and at end of treatment. Subsequent assessments always include K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, alkaline phosphatase, bicarbonate, phosphorus, glucose, urea or BUN, albumin, and total protein BUT, lipase, total cholesterol, HDL, LDL, triglycerides should be obtained on the first day of odd numbered cycles only.

5 Coagulation - PT or INR, PTT. Patient entering the study while receiving anti-coagulation therapy or those who have the initiation of an anti-coagulation therapy should have their coagulation test performed on a weekly basis.

6 Patients must be fasting overnight for at least 8 hours. Additional measurements may be performed as clinically indicated.

7 Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

8 Screening radiological assessments should be performed within 4 weeks of the first dose. Radiological tumor assessment should be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks of combination therapy (first restaging at the end of week 8), until progression of disease or end of treatment. All assessments should be performed within ±7 days of the scheduled day of assessment. The assessment at the end of treatment visit is only to be performed if the prior assessment occurred ≥ 21 days before.

9 Biopsies will be done at Screening, Cycle 1 Day 15, and within 14 days of any radiographic examination documenting disease progression by RECIST from all patients with visible or palpable disease unless the PI determines that a biopsy would pose an unacceptable risk to the patient.

10 Echo/MUGA will be performed at baseline and every 4 cycles, or more often as clinically indicated.

11 ECG will be performed at baseline and (+/- 2 days) on cycle 1 day 15, on cycle 2, 3, and 4 day 1, and every 3 months thereafter in accordance with the manufacturer"s standard-of-care recommendations for vemurafenib

12 Laboratory assessments including hematology, blood chemistries, and fasting blood glucose do not need to be repeated prior to the first dose of BKM120 if screening laboratories were performed within 72 hours of C1D1.

13 If toxicity is present at C1D15, C1D22 visit may be done at the discretion of the physician.

Note: A Brain MRI may be performed at screening and/or at any time during the study as clinically indicated

3.4.2 Efficacy assessments

Patients will undergo systemic imaging with a contrast-enhanced CT scan of the chest, abdomen, and pelvis (or a whole body PET/CT scan if this scan includes a CT resolution that is comparable to standard institutional protocols for CT alone) with 28 days prior to the initiation of therapy (baseline imaging) and on the last day of every even-numbered treatment cycle(+/- 3 days). Imaging assessments will be made by a radiologist, and final assessment using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) will be made by the PI [37,38]. Any documentation of a PR or CR in a target or non-target lesion must be confirmed by a repeat scan at least4 weeksafter the initial scan indicating the PR or CR. The PI bears the final responsibility for determining tumor response and progression.

3.4.3 Laboratory evaluations

Pregnancy Test

A serum pregnancy test (β-HCG) is required for all women of child-bearing potential at screening, within 72 hours prior to the first dose of BKM120. Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [***for US only***: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Hematology

Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell (RBCs), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count.

Coagulation Profile

The coagulation profile includes prothrombin time or INR, and activated partial thromboplastin time.

Blood chemistry

Biochemistry includes the following parameters: urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, magnesium, phosphorus, glucose, albumin, total protein, total bilirubin (direct and indirect), amylase and lipase, GGT, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, AST (SGOT), ALT (SGPT), and uric acid, lactic dehydrogenase (LDH), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides are required at baseline and at end of treatment. Subsequent assessments always include K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, alkaline phosphatase, bicarbonate, phosphorus, glucose, urea or BUN, albumin, and total protein BUT, lipase, total cholesterol, HDL, LDL, triglycerides should be obtained on the

first day of odd numbered cycles only. C1D-7assessments may be performed up to 72 hours prior to the scheduled visit. Cycle 1 draws may occur within 24 hours prior to the scheduled visit. All other draws should occur within 3 days of the intended visit. Because accurate serum glucose and lipid measurements are required; patients should be fasting at the time of the blood sampling.

Glucose monitoring (FPG, C-peptide, and HbA_{1C})

Fasting plasma glucose (FPG), C-peptide, and HbA_{1C} will be assessed. Patients must be fasting overnight for at least 8 hours prior to the blood draw. The study personnel will ask the patient whether he or she has been fasting, which will be captured in the eCRF as well.

$HbA_{1c}$and C-peptide will be measured at screening and on Day 1 of every third treatment cycle starting with Cycle 2 Day 1 and at EOT.

Urinalysis

Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity) and will be performed at screening visit and EOT visit. A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

This must be supplemented with laboratory quantification of any potentially relevant abnormalities.

3.4.4 Clinical evaluations

3.4.4.1 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

3.4.4.2 Physical examination

Physical examination will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

3.4.4.3 Neuropsychiatric assessments

Patient self-rating mood questionnaires for anxiety and depression (PHQ-9, GAD-7) will be applied at:

- Screening
- Days 1 and 15 of Cycle 1
- Day 1 and 15 of Cycle 2
- Day 1 of Cycle 3 and subsequent cycles (only for patients who have not shown mood alterations during the first 2 cycles, patients who did should continue to fill out the questionnaire on a weekly base).

- End of Study treatment

Additional assessments may be done according to the clinical judgment of the Investigator. Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study. Instructions on how to instruct the patient to complete the questionnaires as well as how to determine the scores will be provided together with each instrument.

3.4.4.4 Performance status

Performance status will be assessed at screening and per the visit schedule using the Eastern Cooperative Oncology Group (ECOG) performance scale.

3.4.5 Additional evaluations

3.4.5.1 ECG/ECHO

A standard 12 lead ECG is to be performed at screening and significant findings must be recorded. An echocardiogram (ECHO) or MUGA will be performed to assess eligibility. ECHO/MUGA will be repeated at Cycle 4 and then every 4th cycle thereafter.

3.4.5.2 Brain imaging

An MRI of the brain with gadolinium maybe performed during screening and patient with untreated or symptomatic brain metastases will be excluded from participation in this trial. Patients with asymptomatic, treated brain metastases with documented radiographic stability over at least 4 weeks may participate in this trial. For all patients enrolled on the trial, additional MRI imaging of the brain may be obtained as clinically indicated.

3.4.6 Drug levels and pharmacokinetic assessments

Data regarding the preclinical and clinical pharmacology of vemurafenib are presented in section 1.2.1.3 and 1.2.3 respectively. Data regarding the preclinical and clinical pharmacology of BKM120 are presented in section 1.4.1.3 and 1.4.2.1 respectively. All BKM120 pharmacokinetic analysis will be performed by Novartis (refer to Appendix 4 for details) and vemurafenib analysis will be performed at UCSF (refer to Appendix 5 for details).

Phase 1, Part A

Historical controls for PK of vemurafenib alone are well established and vemurafenib has minimal hepatic metabolism[4]. Pharmacokinetic measurements of serum levels of BKM120 after single dose will be made during a 7-day lead-in (day -7, t = 0, 1, 2, 6 hrs +/- 15 minutes; day -4 at 72 hrs post-dose +/- 1 hour). Serum levels of BKM120 and vemurafenib will be assessed on cycle 1 treatment day 1 (t = 0, 1, 2, 6 hrs +/- 15 minutes) and day 15 (t = 0, +/- 1 hour) as well as trough levels (t = 0 +/- 1 hour) on day 1 of cycles 2, 3, and 4. Vemurafenib is a weak CYP3A4 inducer and BKM120 is primarily metabolized by CYP3A4. Therefore, the effect of vemurafenib on BKM120 serum levels is of particular interest.

Phase 1, Part B

Serum levels of BKM120 and vemurafenib will be assessed on cycle 1 treatment days 1 (t = 0, 1, 2, 6 hrs +/- 15 minutes) and day 15 (t = 0, +/- 1 hour) as well as trough levels (t = 0 +/- 1 hour) on day 1 of cycles 2, 3, and 4.

Phase 1, Parts A & B

At each sample time point, two aliquots (2 mL each) of whole blood will be collected in EDTA blood collection tubes and the exact time of the dose and the blood draw will be noted. Detailed sample collection and shipping instructions are given in Appendices 4 and 5. Patients should take the daily doses of BKM120 and the first dose of vemurafenib in the morning. Patients must fast forat least 2 hours after a light breakfast (morning meal) before taking BKM120 and vemurafenib. Vemurafenib and BKM120 should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the capsules as a whole and not chew or crush them. Patients should continue to fast for 2 hours after the administration of the morning doses. PK measurements will be compared to historical controls for BKM120 and vemurafenib individually with the goal of comparing peak and trough exposure levels.

3.4.7 Correlative studies and pharmacodynamic assessments

Biopsies of palpable melanoma lesions and nodal metastases will be taken at baseline, on Cycle 1 Day 15 (+/- 3 days), and within 14days of radiographic progression of disease. In addition, existing paraffin-embedded biopsy specimens will also be obtained for analysis and archival. Biopsies for patients with cutaneous, subcutaneous, and palpable nodal metastatic disease may be waived if the PI believes that such biopsies would pose an excessive risk to the patient. Imaging guided biopsies of other metastatic sites are optional and permitted in patients without visible or palpable disease unless the PI believes that such a biopsy would pose an excessive risk to the patient. For skin lesions, punch or core biopsies are preferred. For other lesions, core biopsies are preferred and an attempt should be made to obtain 3 cores if core biopsies are selected. Fine needle aspiration is permitted with punch or core biopsies are not feasible. At the time of tumor progression, biopsies should be taken from both progressing and non-progressing lesions if feasible.

Portions of all new tumor biopsy specimens will be immediately immersed in formalin and subsequently embedded in paraffin and additional tissue will be flash-frozen and stored at -70 ^{o}Cuntil the time of analysis. Paraffin embedded biopsies will be stored at room temperature. Pre-treatment melanoma tumor specimens will be analyzed by PCR to confirm the presence of a $BRAF^{V600E}$or $BRAF^{V600K}$ mutation and to assess for concurrent mutations of NRAS. Specific correlative analyses are outlined below. Any remaining tissue specimens may be archived for future studies that may include but that are not limited to nucleic acid sequencing, microarray analysis, and immunohistochemistry.

6-month PFS as a function of PTEN expression

Our hypothesis is that patients with PTEN loss at baseline will be more likely to survive for 6 months without disease progression. PTEN expression will be assessed as present or absent using immunohistochemical staining for PTEN. Pre-treatment tissue for PTEN IHC will be available for all patients (estimate N = 46) since the availability of pre-treatment tissue for BRAF

genotyping is required. PTEN staining in tumor specimens will be graded as "present" or "absent" for each patient by a collaborating pathologist. Attainment of 6 month PFS as a function of PTEN status will be assessed using Fisher"s exact test.

For PTEN and pS6 IHC, paraffin-embedded sections will be deparaffinized, rehydrated, and subjected to heat-induced antigen retrieval. Sections will be incubated with appropriate primary antibody (PTEN: Cell Signaling D4.3, 1:50 dilution; phospho-S6 Cell Signaling Polyclonal, 1:200 dilution) and incubated for 45 minutes. After overnight incubation with a secondary polyclonal rabbit antibody, slides will be developed using 3-3′-diaminobenzidine chromogen and counterstained with hematoxylin[39].

Change in phospho-S6 as a function of 6-month PFS

Our hypothesis is that patients surviving for 6 months without disease progression will demonstrate a larger decrease in PI3K pathway activity as assessed by IHC for phopsho-S6 than those patients with disease progression or death prior to 6 months. The change in pS6 will be determined by comparing H-scores to quantify pS6 protein levels by IHC prior to treatment at after 8 weeks of treatment[40,39]. The H-Score will be calculated for staining of tumor cells using the following formula; H-Score = (% at 0) * 0 + (% at 1+) * 1 + (% at 2+) * 2 + (% at 3+) * 3. Thus, this score produces a continuous variable that ranges from 0 to 300. The change in phospho-S6 staining will be determined as follows: ΔpS6 = (H4w-H0)/H0. Patients will be categorized based on whether or not they survived for 6 months without disease progression. ΔpS6 over the first 8 weeks of treatment will be compared between the two groups using the Wilcoxon rank-sum test.

Gene expression profiles of PI3K and MAPK signaling in response and progression

Our hypotheses are: 1. Treatment response by RECIST v1.1 criteria after 8 weeks of treatment will be associated with an absence of PI3K and MAPK signaling as assessed by gene expression profiling and 2. Disease progression is associated with activation of either pathway. Gene expression profiling has emerged as in important tool for elucidating mechanisms of resistance to BRAF inhibitors in melanoma by identifying gene signatures of oncogenic pathway activation in an unbiased manner[41]. cDNA will be derived from RNA extracted from flash-frozen tissue specimens. Gene expression will be determined using GeneChip Human Gene 1.0 ST Arrays (Affymetrix) on cycle 3 day 1 (+/- 3 days) and within 7 days of determination of tumor progression. These profiles will be referenced to the profile of tumor tissue obtained prior to the initiation of treatment. Expression data will be normalized and background-corrected. Clustering will be performed with MeV 4.4. Differentially expressed genes will be identified using significance analysis of microarrays (SAM) with the R package. To identify and rank pathways enriched among differentially expressed genes, P-values (Fisher"s exact test) will be calculated for gene sets with at least 20% differentially expressed genes. Curated gene sets of canonical pathways including PI3K and MAPK in the Molecular Signatures Database (MSigDB) will be used as the comparator. Gene expression signatures consistent with MAPK, PI3K, or alternate pathways activation will be confirmed by RT-PCR and immunohistochemistry for phospho-protein levels such as pS6 and pERK. Our initial goal is to perform microarray analysis on matched biopsy specimens from a total of 10 patients: 5 who meet the 6 month PFS endpoint, and 5 with early disease progression within 4 months of the initiation of treatment. Until these patients have been identified, all patients with visible or palpable disease will undergo pre-

treatment biopsies. Additional biopsies and additional analyses may be performed at the discretion of the PI.

3.5 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

3.6 Safety monitoring plan

3.6.1 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations. Dermatologic assessments will be performed at screening, on week 3 day 1, and at every 8 week intervals thereafter.

These assessments should be performed within ±1 day (during DLT period) or ±3days (all subsequent cycles) of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

3.6.2 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about BKM120 can be found in the Investigators‟ Brochure and additional data regarding vemurafenib can be found in the published literature. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Adverse Event Monitoring: Adverse events (AEs) will be recorded on the OnCoreeResearch database, all grade 3-5 expected and unexpected AEs will be recorded and updated at each visit.

3.6.3 Serious adverse events

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient‟s general condition
  - is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring

- after the patient has provided informed consent and until 4 weeks after the patient has stopped study treatment/participation
- after the patient is randomized and until 4 weeks after the patient has stopped study treatment
- after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in

treatment to a fixed dose of concomitant medication) and until 4 weeks after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

3.6.4 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee (DSMC)

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 24 business hours of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF's Committee on Human Research (CHR)

The Investigator must report events meeting the CHR definition of "Unanticipated Problem" (UP) within 10 working days of his/her awareness of the event.

Guidance on Adverse Event Reporting to the CHR is available online at the *UCSF Human Research Protection Program* website.

Expedited Reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeframe for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than **7 calendar days** after the Investigator"s initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report must be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

The investigator (or designee) should prepare *Form FDA 3500A (MedWatch)*detailing the event, and contact the Institutional Trials Unit for assistance in the preparation of the IND Safety Report.

For additional information and guidance on IND Safety Reports, please refer to FDA"s Guidance document*Safety Reporting Requirements for INDs*.

Reporting to Genentech and Novartis

Genentech

Serious AE and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within 24 hours of the Awareness Date.The completed MedWatch/case report should be faxed immediately upon completion to**Genentech Drug Safety** at:

(650) 225-4682OR (650) 225-5288

Additional Reporting Requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the vemurafenib will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report Genentech.
- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

Novartis

All events must be reported by FAX (888-299-4565) to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence using an SAE Report form provided by Novartis**.** This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days. The original copy of the SAE Report and the fax confirmation sheet must be kept within the Study File.

Relevant follow-up information should be submitted to Novartis Drug Safety as soon as it becomes available. Follow-up information is sent to the same person(s) to whom the original

SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the BKM120 or vemurafenib Investigators" Brochure or Package Insert (new occurrence) and is thought to be related to the study drugs, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

3.6.5 Oversight and monitoring

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data in each cohort
- Review of all serious adverse events
- Minimum of a yearly audit

3.6.5.1 Monitoring and reporting guidelines

Investigators will conduct continuous review of data and patient safety at monthly study group or site committee meetings where the results of each patient"s treatment are discussed and the discussion is documented in the minutes. The discussion will include the number of patients, significant toxicities as described in the protocol, doses adjustments, and observed responses. All grade 3-5 AEs and SAEs will be entered in the HDFCCC OnCoreClinical Trial Management System (CTMS).

Review of Adverse Event Rates: If the study has an increase of unexpected or expected Adverse Event grade 3 or 4 above the rate reported in the Investigational Brochure or package insert, the increase rate of AEs will be reported to the DSMC at the time of Identification. The Chair and PI will discuss the finding and proceed with a written course of action. If at any time the Investigator stops enrollment or stops the study due to safety issues the DSMC Chair and Administrator must be notified within 24 business hours via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data Safety Monitoring Committee Contacts:

DSMC Chair:	Thierry Jahan, MD	DSMC Monitors - address
Phone:	415-353-2745	Box 1297
Email:	venook@cc.ucsf.edu	UCSF Helen Diller Family
Address:	Box 1705	Comprehensive Cancer Center
	UCSF Helen Diller Family	San Francisco, CA 94115
	Comprehensive Cancer Center	
	San Francisco, CA 94143	

3.6.6 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis. The pregnancy should be followed up for 3 months after the termination of the pregnancy 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 Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of 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.

The team needs to prepare information for the female partner of the male patient on required contraception. This information needs to be given to the male patient at the ICF signing for him to share it with his female partner.

Information for female partners of male study participants

Your male partner is offered to participate in a clinical research study. As a prerequisite to participate in this study your partner must agree to use a condom during intercourse. This is important because test results of the study treatment in pregnant animals indicated that the medicine can harm an unborn baby through the sperm. At the same time it is also important that you do not become pregnant while your partner is taking the medication. Therefore, you should use a highly effective method of birth control (contraception) during the time your male partner receives the study treatment and thereafter for another 3 months. Highly effective methods of contraception are those methods of birth control that have less than 1% of unwanted pregnancy during one year, if used appropriately according to the instructions of the manufacturer.

Those methods are the following:

1. True 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.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the

reproductive status of the woman has been confirmed by follow up hormone level assessment.

3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that patient.
4. Use of a combination of any two of the following (a+b):
   a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
   b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- Oral contraception, injected or implanted hormonal methods are not allowed as BKM120 potentially decreases the effectiveness of hormonal contraceptives.
- Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for 5 T1/2 (8 days) after stopping treatment and for additional 12 weeks (3 months in total after study drug discontinuation) and should not father a child in this period.

For details on the most appropriate contraception you may talk to your regular doctor, or if check that your male partner agrees with the study doctor.

If you get pregnant despite taking the birth control precautions, please ask your partner to inform the study doctor as soon as possible. The study doctor will ask your permission to collect information about you, your pregnancy and your child.

4 Protocol amendments, or changes in study conduct

Any change or addition to this protocol requires a written protocol amendment that must be approved by the PRC and the CHR prior to implementation.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is implemented for safety reasons the CHR will be informed immediately.

5 Statistical methods

5.1 Study Design/Endpoints

This is a phase 1/2 clinical trial designed to determine the recommended phase 2 dose of PI3K inhibitor BKM120 in combination with BRAF inhibitor vemurafenib (phase 1) followed by a determination of 6 month progression-free survival rate (phase 2) in patients with BRAF mutant melanoma.

For Phase 1, Part A

This is a single-arm, open-label phase 1 clinical trial. The primary endpoint for phase I, part A is the RP2D of vemurafenib twice daily and BKM120 daily in BRAF mutant melanoma patients with no prior exposure to potent BRAF inhibitorsand the primary safety endpoint is DLT. Phase 1 dose levels are described in *Table 5* and details regarding dose escalation and identifying the RP2D are given in section 3.3.2.1.

For Phase 1, Part B

The primary endpoint for phase 1, part B is the RP2D of vemurafenib twice daily in BRAF mutant melanoma patients with prior progression of disease on potent BRAF inhibitors and BKM120 daily and the primary safety endpoint is DLT.

For the Phase 2 portion

The primary endpoint of the Phase 2 portion is the progression-free survival rate at 6 months. Imaging assessments will be made by a radiologist, and final assessment using Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) will be made by the PI. Any documentation of a PR or CR in a target or non-target lesion must be confirmed by a repeat scan at least 4 weeks after the initial scan indicating the PR or CR. Disease response will be assessed at scheduled visits by diagnostic anatomic imaging, and clinical exam. All patients will be followed for 6 months and proportion of patients that are progression free at 6 months will be calculated.

Secondary Endpoints

Median PFS and OS defined by the Kaplan-Meier method. Tumor progression will be defined using RECIST version 1.1.Analysis of tolerability will be descriptive with reporting of all events by grade that are thought to be possibly, probably, and definitely attributable to study drug. Correlative assessments for PTEN expression, changes in pS6, and gene expression analysis are described in section 3.4.7 along with statistical analysis plans for these assessments.

5.2. Sample Size/Accrual Rate

This study will use the standard 3+3 dose escalation design to determine the RP2D of BKM120 in combination with vemurafenib (phase 1) followed by a single-stage binomial phase 2 design of 37 evaluable patients (any patient receiving at least 75% of prescribed cohort dose during the DLT period) to determine the PFS rate at 6 months.

For the Phase 1 portion

A Phase 1 dose escalation design using the standard 3+3 scheme will be followed and the sample size is not predetermined. We estimate the phase 1 portion of this trial will require a minimum of 2 patients from four predefined dose levels (see *Table 5*) to determine the phase 2 dose (MTD). The estimated maximum number of patients is 24. The final sample size of the study depends primarily on clinical considerations rather than on statistical considerations.

For the Phase 2 portion

The sample size for the phase 2 portion of this study is determined using single-stage binomial design for phase 2 studies. Preliminary data from trials of vemurafenibmonotherapy in advanced melanoma suggest a median PFS of approximately 6 months[4,5,17]. The proposed design will be used to test the null hypothesis that the 6 month PFS rate of the study combination is 50% or less (which would not be clinically desirable) versus the alternative hypothesis that the true 6 month PFS rate is greater 70%, which would be considered clinically meaningful. The maximum total sample size will be 37 in Phase 2 including patients in the phase 1 portion of the study treated at the RP2D.

5.3 Analysis Plan

All patients who received at least 75% of prescribed cohort dose during the DLT period will be considered evaluable. Patients not evaluable will be replaced.

Phase 1 portion of the study

Safety and tolerability will also be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and physical exam. Adverse experiences will be summarized as counts and frequencies for each dose level. Other safety endpoints will be summarized as appropriate. These data are descriptive in nature and statistical analysis tools will not be required. The recommended phase 2 dose will be determined using safety data including DLTs and post-DLT toxicity, the dose-response relationship, and PK data.

Pharmacokinetic data will be acquired as described in section 3.4.6 and average values and standard deviations at each time point will be reported.

Phase 2 portion of the study

The PFS duration is defined as the time from the date of start of protocol therapy to the date of the first documented progression or death due to any cause. A patient who has not progressed or died by the date of the analysis cut-off or when the patient received any further anticancer therapy would have the PFS censored at the time of the last adequate tumor assessment before the first of the cut-off date or of the anticancer therapy date. All patients will be followed for 6 months and proportion of patients that are progression free at 6 months will be calculated. We assume that combination treatment will have at least 70% PFS rate versus the undesirable PFS of <50% at 6 months. The phase 2portion is designed based single stage binomial design with the type I alpha of 5% and the power of 80%. If ≥ 23 patients ultimately achieve 6 months PFS, then further investigation of the drug is warranted.

As secondary efficacy endpoints, the median PFSand OS will be estimated using exact binomial distribution; time to progression will be estimated using Kaplan-Meier methods. The 6-month PFS and 95% confidence intervals will be reported. ORR will be reported as frequencies and proportions with exact 95% confidence intervals from the Binomial distribution. The frequencies of individual toxicities thought to be probably, possible, or definitely related to study drug will be reported as well as the incidence of any grade 3, 4, and 5 toxicities regardless of attribution.

Correlative assessments for PTEN expression, changes in pS6, and gene expression analysis are described in section 3.4.7 along with statistical analysis plans.

6 Procedures and instructions

6.1.1 Publication of results

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 fifteen 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. Principal Investigation/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.

6.1.2 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/REB. 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.

6.1.3 Discontinuation of study

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

6.2 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice and:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)
- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects)

The investigator agrees 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.

6.2.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, will be reviewed by the Committee on Human Research (CHR) (UCSF‟s Institutional Review Board [IRB]). A signed and dated statement that the protocol and informed consent have been approved by the CHR will be providedto Novartis before study initiation. Any amendments to the protocol will be approved by the CHR prior to implementation.

6.2.2 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 willbe submitted by the investigator to the CHR for approval.

6.2.3 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, biweekly conference calls with the participating sites for Phase I dose escalation studies prior to each cohort escalation and at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

6.2.4 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

6.2.5 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

6.2.6 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site‟s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form

- Participating Site IRB membership list
- Participating Site IRB‟s Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

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

References

1. Jemal, A. et al. Cancer Statistics, 2008. *CA Cancer J Clin*58, 71-96 (2008).
2. Barth, A., Wanek, L.A. & Morton, D.L. Prognostic factors in 1,521 melanoma patients with distant metastases. *J. Am. Coll. Surg*181, 193-201 (1995).
3. Davies, H. et al. Mutations of the BRAF gene in human cancer. *Nature*417, 949-954 (2002).
4. Flaherty, K.T. et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N. Engl. J. Med*363, 809-819 (2010).
5. Chapman, P.B. et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. *N Engl J Med* 110605080854063 (2011).doi:10.1056/NEJMoa1103782
6. Uribe, P., Wistuba, I.I. & González, S. BRAF mutation: a frequent event in benign, atypical, and malignant melanocytic lesions of the skin. *Am J Dermatopathol*25, 365-370 (2003).
7. Dankort, D. et al. Braf(V600E) cooperates with Pten loss to induce metastatic melanoma. *Nat. Genet*41, 544-552 (2009).
8. Goel, V.K., Lazar, A.J.F., Warneke, C.L., Redston, M.S. & Haluska, F.G. Examination of mutations in BRAF, NRAS, and PTEN in primary cutaneous melanoma. *J. Invest. Dermatol*126, 154-160 (2006).
9. Tsao, H., Goel, V., Wu, H., Yang, G. & Haluska, F.G. Genetic interaction between NRAS and BRAF mutations and PTEN/MMAC1 inactivation in melanoma. *J. Invest. Dermatol*122, 337-341 (2004).
10. McArthur, G. et al. Molecular analyses from a phase I trial of vemurafenib to study mechanism of action (MOA) and resistance in repeated biopsies from BRAF mutation–positive metastatic melanoma patients (pts). *Journal of Clinical Oncology Abstracts*29, abstract 8502 (2011).
11. Baselga, J. et al. A first-in-human phase I study of BKM120, an oral pan-class I PI3K inhibitor, in patients (pts) with advanced solid tumors. *J Clin Oncol (Meeting Abstracts)*28, Abstract 3003 (2010).
12. Bollag, G. et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. *Nature* (2010).doi:10.1038/nature09454
13. Kaplan, F.M., Shao, Y., Mayberry, M.M. & Aplin, A.E. Hyperactivation of MEK-ERK1/2 signaling and resistance to apoptosis induced by the oncogenic B-RAF inhibitor, PLX4720, in mutant N-RAS melanoma cells. *Oncogene* (2010).doi:10.1038/onc.2010.408
14. Poulikakos, P.I., Zhang, C., Bollag, G., Shokat, K.M. & Rosen, N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature*464, 427-430 (2010).
15. Yang, H. et al. RG7204 (PLX4032), a selective BRAFV600E inhibitor, displays potent antitumor activity in preclinical melanoma models. *Cancer Res*70, 5518-5527 (2010).
16. Lee, J.T. et al. PLX4032, a potent inhibitor of the B-Raf V600E oncogene, selectively inhibits V600E-positive melanomas. *Pigment Cell Melanoma Res*23, 820-827 (2010).
17. Plexxikon Plexxikon Announces Preliminary PLX4032 Phase 2 Data Confirming Substantial Response Rate in Metastatic Melanoma Patients. (2011).at <http://www.plexxikon.com/view.cfm/83/Press-Releases>
18. Weinstein, I.B. & Joe, A. Oncogene addiction. *Cancer Res*68, 3077-3080; discussion 3080 (2008).
19. Katso, R. et al. Cellular function of phosphoinositide 3-kinases: implications for

development, homeostasis, and cancer. *Annu. Rev. Cell Dev. Biol*17, 615-675 (2001).
20. Kim, H.H., Sierke, S.L. & Koland, J.G. Epidermal growth factor-dependent association of phosphatidylinositol 3-kinase with the erbB3 gene product. *J. Biol. Chem*269, 24747-24755 (1994).
21. Ram, T.G. & Ethier, S.P. Phosphatidylinositol 3-kinase recruitment by p185erbB-2 and erbB-3 is potently induced by neu differentiation factor/heregulin during mitogenesis and is constitutively elevated in growth factor-independent breast carcinoma cells with c-erbB-2 gene amplification. *Cell Growth Differ*7, 551-561 (1996).
22. Ma, Y.Y. et al. PIK3CA as an oncogene in cervical cancer. *Oncogene*19, 2739-2744 (2000).
23. Fry, M.J. Phosphoinositide 3-kinase signalling in breast cancer: how big a role might it play? *Breast Cancer Res*3, 304-312 (2001).
24. Roymans, D. & Slegers, H. Phosphatidylinositol 3-kinases in tumor progression. *Eur. J. Biochem*268, 487-498 (2001).
25. Bachman, K.E. et al. The PIK3CA gene is mutated with high frequency in human breast cancers. *Cancer Biol. Ther*3, 772-775 (2004).
26. Broderick, D.K. et al. Mutations of PIK3CA in anaplastic oligodendrogliomas, high-grade astrocytomas, and medulloblastomas. *Cancer Res*64, 5048-5050 (2004).
27. Samuels, Y. et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science*304, 554 (2004).
28. Ohgaki, H. Genetic pathways to glioblastomas. *Neuropathology*25, 1-7 (2005).
29. Zeng, Z. et al. Simultaneous inhibition of PDK1/AKT and Fms-like tyrosine kinase 3 signaling by a small-molecule KP372-1 induces mitochondrial dysfunction and apoptosis in acute myelogenous leukemia. *Cancer Res*66, 3737-3746 (2006).
30. Chow, L.M.L. & Baker, S.J. PTEN function in normal and neoplastic growth. *Cancer Lett*241, 184-196 (2006).
31. Cully, M., You, H., Levine, A.J. & Mak, T.W. Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. *Nat. Rev. Cancer*6, 184-192 (2006).
32. Kwiatkowski, D.J. Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. *Cancer Biol. Ther*2, 471-476 (2003).
33. Bandaru, S.S., Lin, K., Roming, S.L., Vellipuram, R. & Harney, J.P. Effects of PI3K inhibition and low docosahexaenoic acid on cognition and behavior. *Physiol. Behav*100, 239-244 (2010).
34. Polter, A. et al. Forkhead box, class O transcription factors in brain: regulation and behavioral manifestation. *Biol. Psychiatry*65, 150-159 (2009).
35. Beaulieu, J., Gainetdinov, R.R. & Caron, M.G. Akt/GSK3 signaling in the action of psychotropic drugs. *Annu. Rev. Pharmacol. Toxicol*49, 327-347 (2009).
36. Riddle, M.C., Rosenstock, J. & Gerich, J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*26, 3080-3086 (2003).
37. Tsuchida, Y. & Therasse, P. Response evaluation criteria in solid tumors (RECIST): new guidelines. *Med. Pediatr. Oncol*37, 1-3 (2001).
38. Eisenhauer, E.A. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer*45, 228-247 (2009).
39. Schultz, L. et al. Expression status and prognostic significance of mammalian target of rapamycin pathway members in urothelial carcinoma of urinary bladder after cystectomy. *Cancer*116, 5517-5526 (2010).

40. Armstrong, A.J. et al. A pharmacodynamic study of rapamycin in men with intermediate- to high-risk localized prostate cancer. *Clin. Cancer Res*16, 3057-3066 (2010).
41. Nazarian, R. et al. Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. *Nature*468, 973-977 (2010).

Appendix 1 Questionnaires

Table A1. Toxicity grading based on mood questionnaire scores

PHQ-9			GAD-7		
Score	**Severity**	**CTCAE grading**	**Score**	**Severity**	**CTCAE grading**
0-4	None	Normal	0-4	None	Normal
5-9	Mild	Grade 1	5-9	Mild	Grade 1
10-19	Moderate	Grade 2	10-14	Moderate	Grade 2
20-27	Severe	Grade 3	≥ 15	Severe	Grade 3

At Screening, a patient as judged by the investigator or who meets the cut-off score of ≥ 10 inthe PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, will be excluded fromthe study unless overruled by the psychiatric assessment.

During the study, for patients who meet the cut-off score of ≥ 10 (≥ CTCAE grade 2 moodalteration) in either questionnaire, a psychiatrist will be consulted for diagnosis and determination ofmost appropriate medical treatment. For anxiety, this applies only if status has worsened frombaseline. Patients who experience ≥ grade 2 mood alteration will be followed twice weekly bypatient self-rating mood scale and will be seen weekly by the psychiatrist until resolved ≤grade 1 or baseline (for anxiety). Questionnaire responses will be checked by the psychiatristat the weekly visits (until resolution to Grade 1 or baseline (for anxiety).

Table A2. GAD-7 anxiety scale

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "✓" to indicate your answer")	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Column totals: _____ + _____ + _____ + _____

= Total Score _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very Difficult	Extremely Difficult
☐	☐	☐	☐

Table A3. PHQ-9 depression scale

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer"	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things.....	0	1	2	3
2. Feeling down, depressed, or hopeless……..	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much.....	0	1	2	3
4. Feeling tired or having little energy.....…….….	0	1	2	3
5. Poor appetite or overeating.....……	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down……	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television……	0	1	2	3
8. Moving or speaking so slowly that other people couldhave noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.....	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way.....	0	1	2	3
Column totals:	_____ +	_____ +	_____ +	_____
		= Total Score _____		

Appendix 2 Prohibited medications

Table A4. List of prohibited CYP3A Inhibitors and Inducers

Strong CYP3A4,5,7 inhibitors	Moderate CYP3A4,5,7 inhibitors	CYP3A4 inducers
Clarithromycin	aprepitant	Barbiturates
Conivaptan	atazanavir	Carbamazepine
grapefruit juice	cimetidine	Efavirenz
Indinavir	ciprofloxacin	Modafenil
Itraconazole	darunavir	Nevirapine
Ketoconazole	diltiazem	Oxcarbazepine
Lopinavir	erythromycin	Phenobarbital
Mibefradil	fluconazole	Phenytoin
Nefazodone	tofisopam	pioglitazone
Nelfinavir	verapamil	Rifabutin
Posaconazole	amprenavir	Rifampin
Ritonavir	fosamprenavir	St. John's wort
Saquinavir		Topiramate
Telithromycin		troglitazone
troleandomycin		
Voriconazole		

This database of CYP inhibitors was compiled from the Indiana University School of Medicine‟s “Clinically Relevant” Table and from the University of Washington‟s Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase BKM120 AUC > 5-fold, and moderate inhibitors are predicted to increase BKM120 AUC ≥ 2-fold but < 5-fold.

This database of CYP inducers was compiled from the FDA‟s “Guidance for Industry, Drug Interaction Studies;” from the Indiana University School of Medicine‟s “Clinically Relevant” Table; and from (Pursche et al. 2008).

Table A5. List of CYP450 Substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	Adinazolam	felodipine1
cerivastatin	diclofenac	citalopram	alfentanil1,2	fentanyl2
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine1	flunitrazepam
repaglinide	fluvastatin	clomipramine	Alprazolam	fluticasone1
rosiglitazone	glibenclamide (glyburide)	clopidogrel	Amlodipine	lovastatin1
torasemide	gliclazide	diazepam	Aripiprazole	maraviroc1
troglitazone	glimepiride	fluoxetine	Atorvastatin	midazolam1
	glipizide	imipramine	Brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam1	nisoldipine
	irbesartan	mephobarbital	budesonide1	nitrendipine
	ketobemidone	moclobemide	buspirone1	perospirone1
	lornoxicam	omeprazole	Capravirine	quinine
	losartan	pantoprazole	Cerivastatin	sildenafil1
	meloxicam	progesterone	Chlorpheniramine	simvastatin1
	naproxen	quazepam	cyclosporine2	sirolimus1,2
	nateglinide	rabeprazole	darifenacin1	tolvaptan
	piroxicam	sertraline	Diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine2	triazolam1
	S-ibuprofen		ebastine1	
	sulfamethoxazole		eletriptan1	
	tenoxicam		eplerenone1	
	tolbutamide		ergotamine2	
	torasemide		Estazolam	
	valdecoxib		everolimus1	

* This database of CYP substrates was compiled from the Indiana University School of Medicine″s "Clinically Relevant" Table, and from (Zhou et al. 2009)

** CYP3A substrates were compiled from the Indiana University School of Medicine″s "Clinically Relevant" Table; and supplemented by the FDA″s "Guidance for Industry, Drug Interaction Studies" and the University of Washington″s Drug Interaction Database.

1 Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

2 Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

Appendix 3 QT prolonging drugs

Note: If a patient, **PRIOR** to enrollment, is on a chronic treatment with any medication listed in *Table A6*, AND the treatment cannot be discontinued or switched to a different medication prior to starting study drug, then the patient cannot enter the trial (see exclusion criteria).

If a patient, **AFTER** she/he has been enrolled, requires the concomitant use of any medication listed in *Table A6*, then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be monitored.

Table A6. QT prolonging drugs with risk of Torsades de Pointes to avoid

Drug	QT risk(*)	Comment
Amiodarone	known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	known risk for TdP	
Astemizole	known risk for TdP	No longer available in US. CYP3A4 substrate with narrow therapeutic index.
Bepridil	known risk for TdP	Females>Males
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Cisapride	known risk for TdP	Restricted availability; Females>Males. CYP3A substrate with narrow therapeutic index.
Disopyramide	known risk for TdP	Females>Males
Dofetilide	known risk for TdP	
Domperidone	known risk for TdP	Not available in the US.
Droperidol	known risk for TdP	
Halofantrine	known risk for TdP	Females>Males
Haloperidol	known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	Females>Males
Levomethadyl	known risk for TdP	Sensitive CYP3A substrate
Mesoridazine	known risk for TdP	
Methadone	known risk for TdP	Females>Males
Pentamidine	known risk for TdP	Females>Males
Pimozide	known risk for TdP	Females>Males. Sensitive CYP3A substrate with narrow therapeutic index
Probucol	known risk for TdP	No longer available in U.S.
Procainamide	known risk for TdP	
Quetiapine	possible risk for TdP	Sensitive CYP3A substrate
Quinidine	known risk for TdP	Females>Males. Sensitive CYP3A substrate
Sotalol	known risk for TdP	Females>Males
Sparfloxacin	known risk for TdP	

Table A6. QT prolonging drugs with risk of Torsades de Pointes to avoid

Drug	QT risk(*)	Comment
Tacrolimus	possible risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Terfenadine	known risk for TdP	No longer available in U.S. Sensitive CYP3A substrate with narrow therapeutic index
Thioridazine	Known risk for TdP	
Vardenafil	possible risk for TdP	Sensitive CYP3A substrate

(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT

Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Table A7. List of QT prolonging drugs to be used with caution
(Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT)

Drug	QT Risk
Alfuzosin	possible risk for Torsades de Pointes
Amantadine	possible risk for Torsades de Pointes
Amitriptyline	conditional risk for Torsades de Pointes
Azithromycin	possible risk for Torsades de Pointes
Chloral hydrate	possible risk for Torsades de Pointes
Citalopram	conditional risk for Torsades de Pointes
Clomipramine	conditional risk for Torsades de Pointes
Clozapine	possible risk for Torsades de Pointes
Desipramine	conditional risk for Torsades de Pointes
Diphenhydramine	conditional risk for Torsades de Pointes
Dolasetron	possible risk for Torsades de Pointes
Doxepin	conditional risk for Torsades de Pointes
Dronedarone	possible risk for Torsades de Pointes
Felbamate	possible risk for Torsades de Pointes
Flecainide	possible risk for Torsades de Pointes
Fluoxetine	conditional risk for Torsades de Pointes
Foscarnet	possible risk for Torsades de Pointes
Fosphenytoin	possible risk for Torsades de Pointes
Galantamine	conditional risk for Torsades de Pointes
Gatifloxacin	possible risk for Torsades de Pointes
Gemifloxacin	possible risk for Torsades de Pointes
Granisetron	possible risk for Torsades de Pointes
Imipramine	conditional risk for Torsades de Pointes
Indapamide	possible risk for Torsades de Pointes
Isradipine	possible risk for Torsades de Pointes
Levofloxacin	possible risk for Torsades de Pointes
Lithium	possible risk for Torsades de Pointes
Mexiletine	conditional risk for Torsades de Pointes
Moexipril/HCTZ	possible risk for Torsades de Pointes
Moxifloxacin	possible risk for Torsades de Pointes
Nicardipine	possible risk for Torsades de Pointes
Nortriptyline	conditional risk for Torsades de Pointes
Octreotide	possible risk for Torsades de Pointes
Ofloxacin	possible risk for Torsades de Pointes

Table A7. List of QT prolonging drugs to be used with caution

(Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT)

Drug	QT Risk
Ondansetron	possible risk for Torsades de Pointes
Oxytocin	possible risk for Torsades de Pointes
Paliperidone	possible risk for Torsades de Pointes
Paroxetine	conditional risk for Torsades de Pointes
Perflutren lipid microspheres	possible risk for Torsades de Pointes
Protriptyline	conditional risk for Torsades de Pointes
Ranolazine	possible risk for Torsades de Pointes
Risperidone	possible risk for Torsades de Pointes
Roxithromycin*	possible risk for Torsades de Pointes
Sertindole	possible risk for Torsades de Pointes
Sertraline	conditional risk for Torsades de Pointes
Solifenacin	conditional risk for Torsades de Pointes
Tizanidine	possible risk for Torsades de Pointes
Trazodone	conditional risk for Torsades de Pointes
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes
Trimipramine	conditional risk for Torsades de Pointes
Venlafaxine	possible risk for Torsades de Pointes
Ziprasidone	possible risk for Torsades de Pointes

* Not available in the United States

Appendix 4 BKM120 pharmacokinetic analysis

BKM120 sampling and shipping information

- Draw 2 mL into a 5 mL EDTA (K3) coated tube
- Invert the tube gently several times to avoid clotting
- Place the tube into an ice bath at approximately 4°C during the sampling period
- Within 30 min after collection, centrifuge the tube at 3-5°C for 15 min at 1500 to 2000g
- Transfer the plasma into uniquely labeled 2ML SMART SCAN TUBES from Thermo (Reference for rack/48 tubes: Nr. AB1411 or Reference for only 100 tubes: AB-1389) and frozen immediately over solid carbon dioxide (dry ice) or in a freezer at approximately -70°C or below.
- Ship frozen on dry ice to Central Lab

Sample shipment instructions

For each shipment, an inventory of the samples should accompany the shipment. This inventory should include the study ID, subject ID, sample number, visit number scheduled time of collection.

Clearly indicate any missing specimens. The original inventory will be retained at the site in the Investigator‟s file.

All samples will be kept at the temperature specified up to and during the shipment. Unless instructed otherwise, the samples will be packed carefully with suitable packing material and dry ice to keep them frozen.

All shipments should be sent (Monday through Wednesday **only**) by a carrier guaranteeing overnight delivery. The following items should be considered:

- Advise the carrier of the type of service desired, need for personalized door-to-door pickup, and delivery guaranteed within 24 hours.
- Advise the carrier of the nature of the shipment's contents (human biological specimens) and label the package accordingly.
- Indicate Novartis drug code and Study No. on the face of the parcel to be shipped. The parcel also must carry a "dangerous goods" label because of the dry ice (labels supplied by the courier).
- The carrier must be asked to store the parcel(s) in a freezer if shipment is delayed and to replace exhausted dry ice before transportation continues.
- Shipping reservations should be made to allow delivery to Novartis before 16:00 (4 pm) local time Monday to Thursday and before 11:00 (11 am) local time on Friday. Shipments should not be sent between Thursday and Sunday, to prevent arrival over the weekend.

Instructions for shipment of biological samples to Basel

All pharmacokinetic specimens will be kept at the temperature specified in the PK collection and processing section until shipment.

Samples have to be packed according to the ICAO/IATA-Packing-Instructions in an insulated box. To guarantee that the samples remain deep frozen during transport, use about **10 kg of dry ice** per box which will keep the samples frozen during the whole duration of the transport (air freight). Send the parcel to the following.

A shipping log must be included with the shipment.

Ship to:

Novartis Pharma AG
Gerardo de Pierro for WalidElbast
Fabrikstrasse 14 – 3.28.2
CH-4002 Basel,Switzerland
Telephone: +41-79-535 96 32
Fax: +41-61-696 85 84
Email: *ts-dmpk.sample-management@novartis.com*

Please notify the addressee *in advance* of the shipment and indicate:

- Number of the airbill,
- The time and date of shipping and approximate time of arrival,
- Flight Number,
- To whom the shipment is addressed, the study number, carrier and the shipping form number (or equivalent airbill number),
- The sender‟s name, telephone number and alternative contact personnel,
- The total number of cartons and unit weight of each carton,

Also notify the Clinical Trial Leader at Novartis when a shipment has been scheduled.

The samples should be sent at the beginning of a week in order to arrive not later than Thursday.

Appendix 5Vemurafenib pharmacokinetics and correlative studies assessments

Vemurafenib pharmacokinetics

Under the supervision of Drs. Yong Huang and Leslie Floren, vemurafenib analysis will be performed at UCSF.

Vemurafenib sampling and shipping information

- Draw 2 mL into a 5 mL EDTA (K3) coated tube
- Invert the tube gently several times to avoid clotting
- Place the tube into an ice bath at approximately 4°C during the sampling period
- Within 30 min after collection, centrifuge the tube at 3-5°C for 15 min at 1500 to 2000g
- Transfer the plasma into uniquely labeled 2ML SMART SCAN TUBES from Thermo (Reference for rack/48 tubes: Nr. AB1411 or Reference for only 100 tubes: AB-1389) and frozen immediately over solid carbon dioxide (dry ice) or in a freezer at approximately -70°C or below.
- Ship frozen on dry ice to:
  Yong Huang, Ph. D.
  296 Lawrence Street
  University of California, San Francisco
  San Francisco, CA. 94143 – 0912
  Email: *yong.huang@ucsf.edu*
  Phone: 415-476-5220

Correlative studies assessments

Portions of all new tumor biopsy specimens will be immediately immersed in formalin and subsequently embedded in paraffin and additional tissue will be flash-frozen and stored at -70°C until the time of analysis

The primary contact for acquisition and processing of these specimens at UCSF is:

Kim Chong, MD
UCSF Melanoma Fellow
Phone: 353-9986
Email: *chongk@derm.ucsf.edu*

Appendix 6 Multicenter Institutional Studies

6.1 Data and Safety Monitoring Plan* for Multicenter Institutional Study (Phase 1 Dose Escalation)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data in each cohort
- Review of suspected adverse reactions considered "serious"
- Approval of dose escalation by DSMC Chair (or qualified alternate)
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 1 therapeutic studies are designated with a high risk assessment. The data is monitored monthly as subjects are enrolled and includes all visits monitored up through the Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and suspected adverse reactions considered "serious," and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within 2 business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair"s decision, further study accrual is held while further investigation takes place.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject"s treatment at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

<u>Multicenter communication</u>

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)

- Protocol violations
- Other issues affecting the conduct of the study

Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each subject scheduled to be enrolled at a site. Dose level assignments for any subject scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via fax or e-mail.

If a Dose Limiting Toxicity (DLT) arises in a subject treated at a study site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within**1 business day**, after which the UCSF Coordinating Center will notify the other participating sites.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site"s compliance with the protocol, patient safety, and to verify data entry.

Review and Oversight Requirements

Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF"s Clinical Trial Management System.

All clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center"s Site Committee. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within **10 business days** of becoming aware of the event. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" are entered into OnCore® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks.

All suspected adverse reactions considered "serious" should be reported to the UCSF Coordinating Center within **1 business day** of becoming aware of the event or during the next scheduled conference call, whichever is sooner.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the

assigned designee must be notified within **1 business day** from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within **1 business day** of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within **1 business day** via e-mail. The DSMC must receive a formal letter within **10 business days** and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:	Alan Venook, MD	DSMC Monitors
Phone:	415-353-2745	Box 1297
Email:	venook@cc.ucsf.edu	UCSF Helen Diller Family
Address:	Box 1705	Comprehensive Cancer Center
	UCSF	San Francisco, CA 94115
	San Francisco, CA 94115	

* DSMP approved by NCI 09/February2012

6.2 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- DSMC dose escalation approvals with study status summary forms
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator‟s signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

27 April 2012

6.3 Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center at 415-514-6955*or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy

- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract