A Phase II Study of BKM120 (Buparlisib) in Relapsed or Refractory Thymomas

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Table of Contents

Table of Contents 2
List of Abbreviations 4
1 Background 7
1.0 Disease Background 7
1.1 BKM120 7
1.2 PI3K Pathway and Mechanism of Action 8
1.2.1 Preclinical Studies 9
1.2.2 Clinical Experience 12
1.3 Study Rationale 22
2 Study Objectives 26
3 Exploratory Investigational plan 26
3.0 Overall Study Design 26
3.1 Study Population 27
3.1.1 Patient Population 27
3.1.2 Inclusion and Exclusion Criteria 27
4 Treatments 32
4.0 BKM120 Administration 32
4.1 Concomitant Therapy 33
4.1.1 Drugs that are Prohibited 33
4.1.2 Drugs to be Used with Caution 37
4.2 Interruption or Discontinuation of Treatment 40
4.3 Monitoring of BKM120 Suspected Toxicities 46
4.4 Known Undesirable Side Effects of BKM120 47
4.4.1 Neuropsychiatric Events 47
4.4.2 Hyperglycemia 50
4.4.3 Cardiac Events 50
4.4.4 Lung Toxicity/Pneumonitis 51
4.4.5 Liver Toxicity 52
4.5 Study Termination 54
4.6 Visit Schedule and Assessments 55
4.6.1 Visit Schedule 55
4.6.2 Efficacy Assessments 56
4.6.3 Safety Assessments 60
4.6.4 Treatment Compliance 60

4.6.5 Adverse Events....60
4.6.6 Laboratory Evaluations....64
4.6.7 Vital Signs....67
4.6.8 Physical Examination....67
4.6.9 Neuropsychiatric Assessments....67
4.6.10 ECG/ECHO....68
4.6.11 Performance Status....68
4.6.12 Drug Levels and Pharmacokinetic Assessments....68
5 Data Management....68
5.0 Data Collection....68
6 Patient Consent and Peer Judgment....69
7 Statistical Methods....69
7.0 General Considerations....69
7.1 Study Design....69
7.2 Analysis Population....69
7.2.1 Enrolled Population....69
7.2.2 Safety Population....69
7.2.3 Efficacy Population....69
7.3 Sample Size, Accrual and Study Duration....70
7.4 Patient Characteristics....70
7.5 Significant Protocol Violations....70
7.6 Concomitant Medications....70
7.7 Exposure and Compliance....70
7.8 Efficacy Analysis....70
7.9 Safety Analysis....71
7.10 Statistical Analysis of Genetic Data....71
7.11 Interim Analysis....71
7.12 Reporting and Exclusions....71
7.12.1 Evaluation of Toxicity....71
7.12.2 Evaluation of Response....72
8 Data and Safety Monitoring Plan (DSMP)....72
9 References....73
APPENDICES....76

List of Abbreviations

AE	Adverse Event
AKT	See PKB (protein Kinase B)
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatine Kinase
CK-MB	Creatine Kinase - Muscle and Brain isoenzyme
CMV	Cytomegalovirus
CPK	Creatine phosphokinase
CR	Complete Response
CRD	Clinical Research and Development
CS	Cowden Syndrome
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Drug Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
EGFR	Epidermal Growth Factor Receptor
18F-FDG	[18F]-Fluorodeoxyglucose
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization

IgG	Immunoglobulin G
IgM	Immunoglobulin M
HAV	Hepatitis A
HBV	Hepatitis B
HCV	Hepatitis C
HDL	High density lipoprotein
HEV	Hepatitis E
HSV	Herpes Simplex Virus
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection fraction
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
ORR	Overall Response Rate
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
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
WHO	World Health Organization

1 Background

1.0 Disease Background

Thymic malignancies are rare, but represent the third most common type of primary mediastinal tumor (after lymphoma and germ cell tumors) (Temes, et al 1999) and the most common incident tumor type in the anterior mediastinum (Tomaszek 2009). Management is multidisciplinary in nature. Surgical resection is favored when disease is localized, and in the case of early thymoma, can potentially be curative.

However, in the setting of advanced thymoma or thymic carcinoma, the chance of cure is remote, and some combination of chemotherapy and radiation therapy is indicated. Evidence-based guidelines favor combination chemotherapy regimens in the first line, usually containing a platinum agent and some combination of doxorubicin, cyclophosphamide, vincristine and etoposide (National Comprehensive Cancer Network Practice Guidelines in Oncology: Thymic Malignancies, Version 2.2009). Initial response rates in adjuvant or locally advanced settings are good, with response rates over 50% reported in multiple phase II studies such as with PAC regimen of cisplatin, doxorubicin and cyclophosphamide plus radiation, with 70% ORR and 93 months median OS (Loehrer, et al 1997). The ADOC regimen that added vincristine showed an ORR of 91% but with a shorter median OS of 15 months raising question about toxicity (Fornasiero, et al 1990). Regimens not containing doxorubicin tend to have response rate less than 50% in first line therapy (Lemma, et al 2011).

Unfortunately, given the rarity of the disease, there have been few prospective trials of systemic therapy in the advanced or metastatic settings, and while these studies have suggested efficacy with ORRs ranging from 32 to 56%, there are few comparative data except for historical comparisons to consider (Giaccone, et al 1996, Highley, et al 1999, Loehrer, et 2001, Loehrer, et al 2004).

Over 50% of patients with locally advanced or metastatic thymic malignancies may fail initial therapy and therefore require second-line therapy. Biological agents have been investigated for these patients with so far variable rates of response, ranging from 0 to 40%. These included octereotide ± prednisone, imatinib, belinostat, gefitinib, and interleukin-2. (Loehrer, et al 2004, Palmieri, et al 2002, Giaccone, et al 2009, Giaccone, et al 2011, Kurup, et al 2005, Gordon, et al 1995). There is a clear need for better targeted therapies that can target specific mutations (Rajan, et al 2010). One of these targets could be PI3K pathway as outlined in the study rationale in section 1.3.

1.1 BKM120

NVP-BKM120 (BKM120) is a potent and highly specific oral pan-class I PI3K inhibitor that is a 2,6-dimorpholino pyrimidine derivatives. This compound has been studied extensively in non-clinical models and is currently being evaluated in clinical trials.

1.2 PI3K Pathway and Mechanism of Action

The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso, et al 2001). PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. At the structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. The PI3K signaling is modulated by multiple regulators, including growth factors (such as EGF, IGF-1, and FGF), hormones (such as estrogen and thyroid hormone), integrins, intracellular calcium levels, and RAS signaling. PI3K signaling is negatively regulated at the level of PIP3 clearance by phospholipid phosphatases, such as the phosphatase and tensin homologue (PTEN) protein and the inositol 5-phosphatase-2 (SHIP2) protein.

Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006). Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers.

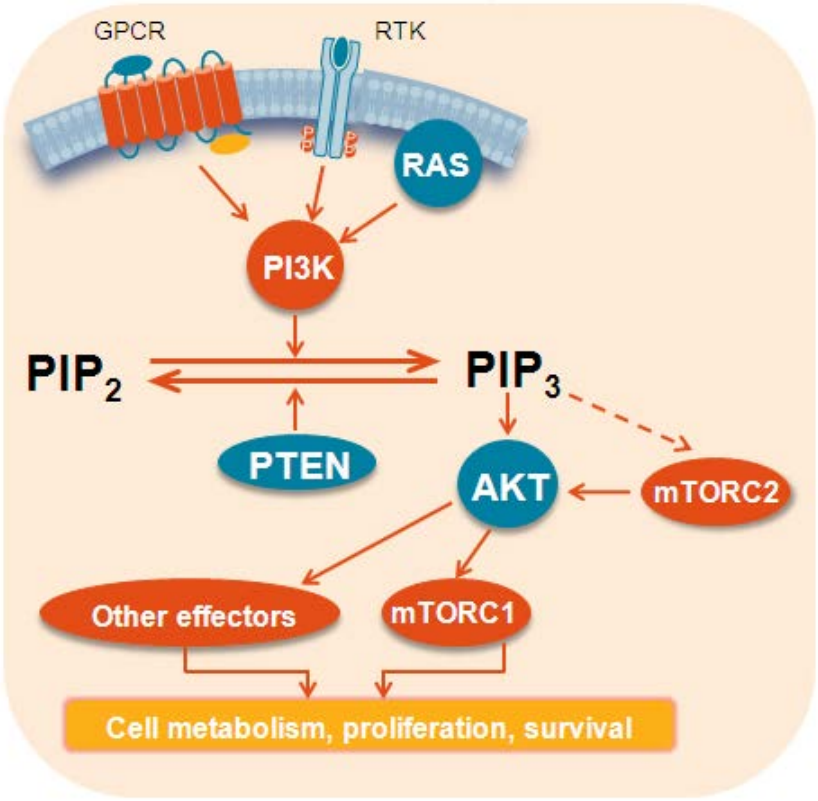
Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to,

a. Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins) or
b. Loss-of-function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g., loss of PTEN expression or function) (Chow 2006, Cully 2006).

Together these observations suggest that PI3K pathway could be a critical therapeutic target for the treatment of patients with advanced solid malignancies who often have limited therapeutic options beyond institutional standard of care. Hence, the pan-PI3K inhibitor BKM120 treatment potentially addresses an unmet medical need in such patients

A schematic representation of these PI3K components is shown in Figure 1-1.

Figure 1-1 Schematic representation of the PI3K pathway



1.2.1 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 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 1-1:

Table 1-1 Inhibitory activities (IC_{50}) of BKM120 against other PI3K or related kinases

Assay	IC_{50} (μM ± SD)	Assay	IC_{50} (μM ± 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® (Class I or III PI3Ks, and PI4Kβ) or TR-FRET assay format (mTOR).

BKM120 significantly inhibits p110α and the most common p110α mutations (H1047R, E454K, E542K), p110β, p110δ and p110γ but 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 (Kwiatkowski 2003). 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.

1.2.1.1 Preclinical Safety

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

1.2.1.2 Pharmacodynamics

BKM120 inhibits wild-type PI3Kα (IC_{50}: 35 nM), with at least 50-fold selectivity towards this target compared to other protein kinases as well as against somatic PI3Kα activating mutants (H1047R-, E542K-, and E545K-p110α), the other three PI3K paralogs as well as the direct downstream effector AKT. BKM120 does not inhibit the related kinases mTOR or Vps34, nor does it inhibit other receptors and ion channels profiled (IC_{50} >10 μM).
BKM120 reduces the phosphorylation of the direct downstream effector Akt in relevant tumor cell lines (e.g., IC50 93 nM for S473P-Akt in Rat1-p110α cells). This biological activity correlates with inhibition of various other downstream signaling components and with antiproliferative activity in a variety of tumor cell lines.

BKM120 demonstrates significant tumor growth inhibition in relevant tumor xenografts in mice and rats when administered orally, including models of renal cell cancer (RENCA, 786-0, Caki-1), glioblastoma multiforme (U87MG), prostate cancer (PC3M), lung cancer (A549, NCI-H1975), ovarian cancer (A2780), colorectal cancer (HCT116, HCT-15) and melanoma (A2058, A375). *In vivo* PK/PD analyses of tumor tissues shows a good correlation between exposure, PI3K pathway blockade (S473P-Akt levels), and anti-tumor activity.

1.2.1.2.1 Nonclinical pharmacokinetics and metabolism

BKM120 showed favorable pharmacokinetic properties in all animal species tested. The absorption of [^{14}C]-BKM120-related radioactivity was >84% in the rat. Oral bioavailability was high in rats (73%), was complete in dogs, and was moderate in monkeys (42%). The estimated steady state plasma volume of distribution (Vss) was high (3.0-3.5 L/kg) in all species tested, suggesting a wide tissue distribution. BKM120 was found to cross the blood brain barrier in rats with a tissue-to-plasma ratio of approximately 2 (Novartis internal data). BKM120 is moderately bound to plasma protein in all species examined (about 80%).

In vitro metabolism studies using human liver microsomes showed that oxidative phase I metabolism of BKM120 was predominantly mediated by CYP3A4 (estimated fm > 0.9). Formation of a BKM120 N-glucuronide conjugate (Phase II metabolism) via the UDP-glucuronosyltransferase-1 family, polypeptide A4 (UGT1A4) was also observed in human liver microsomes supplemented with uridine 5'-diphospho-glucuronic acid (UDPGA). BKM120 and metabolites have a low potential for covalent binding to protein.

BKM120 was determined to be a weak reversible inhibitor of CYP3A4 (IC50 = 8 μM, Ki = 13.4 μM unbound) at concentrations reached in the clinic. BKM120 very weakly inhibited the CYP2C family (2C8, 2C9 and 2C19) with IC50 values ranging from 35-65 μM (34-59 μM unbound). BKM120 did not show time-dependent inhibition of CYP450 enzymes. In GLP toxicology studies, BKM120 exposure in terms of AUC0-24h and Cmax increased in a dose proportional manner in rat and dog. Results from the rat ADME study showed that radioactivity was mainly excreted into the feces. Renal excretion was minor. There was no noticeable drug accumulation in dog or male rats after 13 weeks of daily dosing. There was a slight accumulation in female rats (< 2 fold).

Further information concerning the pharmacokinetic and pharmacodynamic properties of BKM120 may be found in the Investigator Brochure.

1.2.1.2.2 Safety pharmacology and toxicology

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. 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, which was observed in two dog telemetry studies. In rats and dogs, clinical pathology and histopathology findings showed quantitative reductions of lymphoid and erythroid counts and lymphoid tissue hypoplasia.

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. At higher doses in the 2-week dose-range-finding study in rats, there were histopathological findings in both 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 dogs, there was no effect on female sexual organs.

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

Other safety considerations include:

- After up to 2 weeks of treatment with up to 2.5 mg/kg/day of BKM120, alterations in the levels of multiple brain neurotransmitters were seen in rats.
- No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro with BKM120. However, evidence of a genotoxic potential with BKM120 has been seen in vitro and in vivo and is likely due to an aneugenic effect.
- No phototoxic potential or any effect on wound healing has been identified with BKM120 in pre-clinical studies.

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 homeostasis and the risk of increased blood pressure.

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

1.2.1.2.3 Pharmacodynamic biomarkers

The preclinical *in vivo* studies with xenografted tumors in mice indicate that detectable inhibition of AKT phosphorylation, which is an accurate readout of PI3K activity, as well as further suppression of downstream signaling (e.g., phosphorylation of S6) was obtained soon after BKM120 administration. PI3K is known to serve a pivotal role in the regulation of glucose homeostasis, and preclinical studies in which oral glucose and intraperitoneal insulin tolerance tests were performed suggesting post-treatment induction of insulin insensitivity/resistance. Therefore, throughout the trial the circulating levels of several markers for glucose metabolism (e.g., glucose, insulin, C-peptide) will be assessed as an additional measure of PI3K signaling modulation.

1.2.2 Clinical Experience

1.2.2.1 Clinical experience with BKM120

As of September 2012, over 600 patients were enrolled into clinical studies with BKM120 (as single agent or combinations). The Novartis sponsored clinical studies were:

- Phase I single agent studies [CBKM120X2101], [CBKM120X1101], and [CBKM120Z2102]
- Phase II single agent studies [CBKM120C2201] and [CBKM120D2201]
- Phase I combination studies [CBKM120B2101], [CBKM120X2107], [BKM120E2101], [CBEZ235A2118], [LDE225X2114], [CSTI571X2101], and [CMEK162X2101].

- Phase II combination studies [CBKM120F2202]
- Phase III combination study [CBKM120F2302]

For the interest of the current protocol, results presented below will focus on phase I single agent studies ([CBKM120X2101], [CBKM120X1101]), and phase I combinations in breast cancer patients ([CBKM120X2107], [CBEZ235A2118]). Please refer to the current version of the IB for more detailed information.

1.2.2.1.1 Human safety and tolerability data

Study recruitment in study [CBKM120X2101] has been completed with forty (40) patients included in the dose escalation phase at 6 dose levels (all once daily) (12.5 mg (1 patient); 25 mg (2), 50 mg (5), 80 mg (11), 100 mg (17), 150 mg (4)) . Dose limiting toxicities were hyperglycemia, skin rash, epigastric pain, mood disorder, joint pain. The MTD for BKM120 given as a single agent, once daily was established at 100 mg/day (Bendell 2012). Forty-three additional patients were treated in the expansion cohort at 100 mg/day. At the cut-off date of 4th July 2011 (Graña 2011), patient characteristics of 82 patients analyzed were as follows: median age 55 years (range 30–78); ECOG performance status 0/1/2 for 35/46/1 patients, respectively. The safety experience for this single agent trial of BKM120 is described in Table 1-2:

Table 1-2 Most frequent AEs (≥ 15%) related to study drug in study CBKM120X2101 (n=81):

Event	All grades	Grade 3/4
Fatigue/asthenia	**31(38.3%)**	**3 (3.7%)**
Decreased appetite	**24 (29.6%)**	**-**
Diarrhea	**24 (29.6%)**	**3 (3.7%)**
Hyperglycemia	**24 (29.6%)**	**4 (4.9%)**
Nausea	**24 (29.6%)**	**-**
Rash	**22 (27.2%)**	**4 (4.9%)**
Mood altered/emotional disorder/affective disorder	**17 (21.0%)**	**4 (4.9%)**
Transaminases increased	**16 (19.8%)**	**9 (11.1%)**
Anxiety	**14 (17.3%)**	**1 (1.2%)**
Depression	**14 (17.3%)**	**1 (1.2%)**

A second single agent trial, [CBKM120X1101] was a phase I dose escalation study in Japanese patients with advanced solid tumors with dose levels ranging from 25 to 100mg/day (Doi 2011). Enrolment of 15 patients has been completed, including 9 patients at 100 mg/day. One DLT (G4 hepatic function abnormal) was observed in the 100 mg/day group. The most common G3 or G4 adverse events occurring in at least 2 patients were hepatic function abnormal in 6 patients including transaminase increase in 2 patients, G3 anemia in 2 patients, hypokalemia in 2

patients. The recommended phase 2 dose (RP2D) for Japanese patients has been determined at 100 mg/day, as in the western population.

The safety and efficacy of BKM120 combined with trastuzumab in patients with relapsing HER2-overexpressing BC who have previously failed trastuzumab are being explored in a phase Ib/II, multi-center study [CBKM120X2107]. The combination of BKM120 and trastuzumab was shown to be tolerable, and with one dose-limiting toxicity (G3 asthenia) the MTD for BKM120 was declared at 100 mg/day (Saura 2011). Among the 18 patients evaluated in the PhIb part, the following G3/G4 AEs were observed: asthenia, ALT elevation, hyperglycemia, mood alteration, affective disorder, hypersensitivity, photosensitivity reaction, and rash. These AEs were all short-lived and reversible with either dose interruption or modifications as needed. In the phase II portion of the study, as of June 2012, 53 patients have been enrolled and received BKM120 at the recommended phase 2 dose (RP2D) of 100 mg/day in combination with trastuzumab (Pistilli ESMO 2012). Overall the treatment was well tolerated. Most common AEs (>15%) included gastro-intestinal toxicity (e.g. diarrhea, nausea, stomatitis), rash, fatigue, transaminase increase, hyperglycemia, depression and anorexia. No G4 AEs have been reported. Most common G3 treatment related AEs included transaminase increase (~10%), rash (9%) and fatigue (6%), and were consistent with phase Ib findings with as well as single agent BKM120.

Details on liver toxicity, mood alterations, pneumonitis, hyperglycemia, skin rash and hypersensitivity as side effects of BKM120 are presented below.

Liver Toxicity

Liver toxicity has been analyzed based on a search of multiple MedDRA event terms and is presented in Table 1-3. Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly transaminase enzyme increases (ALT and/or AST). Data suggest a higher rate of grade 3/4 liver enzyme elevations in Japanese patients (44.4%) in [CBKM120X1101] study, however, the number of patients (9 patients) treated at 100 mg in this study was limited. Transaminase elevations typically occur during the first 6 to 8 weeks of treatment start.

Table 1-3 Number of patients with liver toxicity

Table 1-3 Number (%) of patients with Liver toxicity, regardless of study drug relationship, by preferred term and treatment - occurred at 100 mg / day in ongoing BKM120 studies

Study Number (n= number of patients treated with 100 mg/d BKM120)	All grades n (%)	Grade 3/4 n (%)
Single agent studies		
CBKM120X2101 (n=55)	22 (40.0%)	16 (29.1%)
CBKM120X1101 (n=9)	4 (44.4%)	4 (44.4%)
CBKM120C2201 (n=70)	29 (41.4%)	19 (27.1%)
CBKM120D2201 (n=38)	7 (18.4%)	3 (7.9%)
Combination studies		
CBKM120X2107 (phase I n=12)	4 (33.3%)	4 (33.3%)
CBKM120X2107 (phase II n=53**)	21 (39.6%)	13 (24.5%)
CBEZ235A2118 (n=22)	1 (4.5%)	0
CBKM120B2101 (n=16)*	5 (31.3%)	1 (6.3%)

These numbers include multiple event terms reflecting liver toxicity: SMQs Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; Hepatitis, non-infectious; Liver related investigations, signs and symptoms (narrow scope)
*Data corresponding to MTD defined to be 70mg QD (in this study no patient was treated at 100mg)
** This number includes 3 patients who were treated with trastuzumab but did not receive treatment with BKM120.

Although transaminase increases are relatively common, only a few of the patients with LFT alterations had other simultaneous observations related to impaired liver function (e.g. bilirubin increase or clinical symptoms). Based on these findings, conservative inclusion criteria and guidelines to monitor and to follow patients with LFT alterations (including dose and schedule modifications) are currently implemented in study protocols investigating BKM120. Please refer to the respective inclusion/exclusion criteria, and Section 4.4.5.2 in this protocol for more detailed guidelines.

A recent liver safety review across Novartis-sponsored trials with BKM120 identified several potentially drug-induced liver toxicity (DILI) cases (e.g. AST/ALT >3.0 x ULN and TBL >2.0 x ULN at any time during the treatment, regardless of causality. Upon medical review, most of these cases occurred in the context of disease progression in terminally ill, advanced cancer patients and/or were confounded by other causes. However, six of these DILI candidates were consistent with Hy's law criteria (e.g. AST/ALT >3.0x ULN and TBL >2.0xULN in the absence of cholestasis and other explanatory causes) with probable causal relationship to study treatment. Five of these cases were enrolled in study CBKM120F2302 in combination with fulvestrant, and one in combination with the investigational drug LDE225 (sonidegib). All patients have recovered upon treatment discontinuation except one patient for whom no data is available since the patient refused to return for safety follow-up.

Mood disorders

Recently, a number of publications demonstrated that the modulation of AKT/GSK3 signaling pathway by neurotransmitters is important for the regulation of behavior (Beaulieu 2009).

Preclinical studies conducted in rats to investigate the effect of BKM120 on different neurotransmitters have shown that repeated administration of BKM120 resulted in an enhanced decrease in glutamate, dopamine, serotonin and epinephrine as well as in an enhanced increase in GABA and HIAA.
Psychiatric side effects events have been reported in patients treated with BKM120 and are currently under investigation. The current data does not allow the identification of any sign or symptom which could predict patient susceptibility to BKM120 induced psychiatric disorders.
A broad range of AEs including (but not limited to) depression, anxiety, mood alteration, confusion, affective disorders, insomnia, hallucination, panic disorders, irritability or difficulties to concentrate have been reported.
Considering the initial symptoms reported during the first-in-man [CBKM120X2101] study, mood disorders have been analyzed based on HLGT 'Mood disorders and disturbances NEC' or HLGT 'Personality disorders disturbances in behavior' or HLGT "Psychiatric and behavioral symptoms NEC" or HLGT "suicidal and behaviors NEC". The frequency of mood disorders thus defined, regardless of study drug relationship, ranged from 6.3% in [CBKM120B2101] study to 50.0% in dose escalation part of [CBKM120X2107] study, however, the majority of events were of grade 1 or 2 severity (Table 1-4).

Table 1-4 Number of patients with mood disorders

Table 1-4 Number (%) of patients with Mood disorders, regardless of study drug relationship, by preferred term and treatment occurred at 100 mg / day in ongoing BKM120 studies

Study Number (n= number of patients treated with 100 mg/d BKM120)	All grades n (%)	Grade 3/4 n (%)
Single agent studies		
CBKM120X2101 (n=55)	16 (29.1%)	2 (3.6%)
CBKM120X1101 (n=9)	4 (44.4%)	0
CBKM120C2201 (n=70)	12 (17.1%)	0
CBKM120D2201 (n=38)	5 (13.2%)	2 (5.3%)
Combination studies		
CBKM120X2107 (phase I n=12)	6 (50.0%)	2 (16.7%)
CBKM120X2107 (phase II n=53**)	17 (32.1%)	4 (7.5%)
CBEZ235A2118 (n=22)	7 (31.8%)	2 (9.1%)
CBKM120B2101 (n=16)*	1 (6.3%)	0

*Data corresponding to MTD defined to be 70mg QD (in this study no patient was treated with BKM120 at 100mg)
** This number includes 3 patients who were treated with trastuzumab but did not receive treatment with BKM120.

Therefore, patients must be regularly and closely monitored for signs and symptoms of neuropsychiatric disorders with particular attention to changes in mood and personality. To support the identification and the assessment of psychiatric disorders, two self-assessment questionnaires, the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), are part of the protocol. Any AEs (symptom/diagnosis) should be accurately reported using CTCAE toxicity/grading. A consultation with a psychiatrist is strongly

recommended for any psychiatric adverse event grade ≥ 1. Protocol guidelines further disqualify patients with an active and/or history of major psychiatric disorder. Please refer to the respective inclusion/exclusion criteria.

Lung Toxicity/ Pneumonitis

Lung changes compatible with pneumonitis have not been observed in the preclinical setting. Among the current studies, pneumonitis was reported in five cases and interstitial lung disease in one further case. One case of pneumonitis had a fatal outcome in a complex clinical context, combining progression of lung metastases and possible infection with pneumocystis jeroveci or cytomegalovirus. Apart from this fatal case, the conditions were resolved or improving at the latest report (except one non-suspected SAE which was unchanged).The currently available data still do not enable a clear assessment about the causal relationship of pneumonitis with BKM120 treatment. Newly appearing or significant changes in pulmonary symptoms (which cannot be explained by the underlying disease), should be carefully followed with appropriate management as per institutional guidelines and the guidelines provided in the protocol.
Please refer to Table 4-8 for more detailed guidelines on the diagnosis and management of Pneumonitis.

Hyperglycemia events

The PI3K/AKT pathway plays a significant role in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycemia is considered as an “on target” effect of BKM120. Regular monitoring of FPG, HbA1c, and insulin C-peptide is implemented in BKM120 protocols to evaluate this pharmacodynamic effect. Transient increases of plasma glucose levels have been reported commonly in patients treated with BKM120. Hyperglycemia observed at 100 mg/day, regardless of study drug relationship, in ongoing BKM120 studies are summarized in Table 1-5.

Table 1-5 Number of patients with hyperglycemia

Table 1-5 Number (%) of patients with Hyperglycemia (narrow search), regardless of study drug relationship, by preferred term and treatment occurred at 100 mg / day in ongoing BKM120 studies

Study Number (n= number of patients treated with 100 mg/d BKM120)	All grades n (%)	Grade 3/4 n (%)
Single agent studies		
CBKM120X2101 (n=55)	19 (34.5%)	4 (7.3%)
CBKM120X1101 (n=9)	3 (33.3%)	1 (11.1%)
CBKM120C2201 (n=70)	40 (57.1%)	16 (22.9%)
CBKM120D2201 (n=38)	12 (31.6%)	6 (15.8%)
Combination studies		
CBKM120X2107 (phase I n=12)	6 (50.0%)	3 (25.0%)
CBKM120X2107 (phase II n=53**)	16 (30.2%)	3 (5.7%)
CBEZ235A2118 (n=22)	6 (27.3%)	2 (9.1%)
CBKM120B2101 (n=16)*	2 (12.5%)	0

These numbers include multiple event terms of a similar meaning to "hyperglycemia": SMQ Hyperglycemia/new onset diabetes mellitus (narrow scope)
*Data corresponding to MTD defined to be 70mg QD (in this study no patient was treated with BKM120 at 100mg)
** This number includes 3 patients who were treated with trastuzumab but did not receive treatment with BKM120.

The highest rate of hyperglycemia (57.1%) was reported in [CBKM120C2201], a Phase II study conducted in patients with advanced endometrial carcinoma, as this was the only study among those listed allowing the enrollment of patients with controlled diabetes mellitus. However, so far, there were only two patients that experienced a grade 4 hyperglycemia, and they both were treated at the highest dose level (150mg/day) in [CBKM120X2101] study. In order to mitigate the potential risk of developing uncontrolled hyperglycemia, only patients with normal glycaemia defined as fasting plasma glucose (FPG) ≤ 120 mg/dL are eligible for study entry. Patients who have a poorly controlled diabetes mellitus defined as (HbA1c >8%) are excluded. In addition, detailed guidelines to monitor patients are recommended including: regular monitoring of FPG to early identify hyperglycemia and prevent acute/sub-acute complications, caution warranted for patients with history of DM, or taking corticosteroids, or with other severe medical conditions (e.g. infections). Hyperglycemia management guidance also includes: dietetic measures and appropriate anti-diabetic medications as per investigator's decision and/or local guidelines, consider oral anti-diabetics such as metformin as first-line treatment for sustained and more severe hyperglycemia (other drugs as appropriate), if sulfonylurea or insulin are initiated, patients should be instructed on how to recognize (and treat) hypoglycemia, for patients with history of DM, management should be based on prior anti-DM treatment.
Detailed guidelines to monitor and manage patients who develop hyperglycemia are provided in Table 4-5.

Skin rash and hypersensitivity

Skin rash is commonly observed in patients treated with BKM120. The rate of skin rash and other related event terms ranged from 18.4% to 41.4% in single agent studies with a

representative number of patients treated with 100mg of BKM120. In one study with nine evaluable patients, seven patients (77.8%) reported such events (Table 1-6). Studies of BKM120 in combination with other agents tended to report slightly higher frequencies (e.g. combination with MEK inhibitor). The skin rashes seen have no typical location or distribution pattern, are mainly papulo-macular (only a minority acneiform) and are frequently associated with pruritus. Events have been reversible after treatment interruption and/ or dose reduction. Effective medications have included antihistamines, topical corticosteroids and/or low-dose systemic corticosteroids (the latter should be used with caution due to the increased risk of hyperglycemia). There have been few cases reported of allergic reactions and DRESS (drug rash with eosinophilia and system symptoms), but these have not been of acute onset or of a severe nature. Complementary information collected suggests that sun exposure may exacerbate the condition and should be avoided; however, genuine photosensitivity reaction has not been confirmed and no phototoxic potential seen pre-clinically. Patients are advised (e.g. in the written patient information) to avoid sun exposure, or take measures to protect themselves from intense sunlight, during study treatment.

Table 1-6 Number of patients with hypersensitivity

Table 1-6 Number (%) of patients with Hypersensitivity, rash, regardless of study drug relationship, by preferred term and treatment occurred at 100 mg / day in ongoing BKM120 studies

Study Number (n= number of patients treated with 100 mg/d BKM120)	All grades n (%)	Grade 3/4 n (%)
Single agent studies		
CBKM120X2101 (n=55)	22 (40.0%)	4 (7.3%)
CBKM120X1101 (n=9)	7 (77.8%)	0
CBKM120C2201 (n=70)	29 (41.4%)	8 (11.4%)
CBKM120D2201 (n=38)	7 (18.4%)	2 (5.3%)
Combination studies		
CBKM120X2107 (phase I n=12)	7 (58.3%)	3 (25.0%)
CBKM120X2107 (phase II n=53**)	23 (43.4%)	9 (17.0%)
CBEZ235A2118 (n=22)	9 (40.9%)	0
CBKM120B2101 (n=16)*	15 (93.8%)	5 (31.3%)

These numbers include multiple event terms reflecting skin rash, hypersensitivity, allergy and photosensitivity conditions
*Data corresponding to MTD defined to be 70mg QD (in this study no patient was treated at 100mg)
** This number includes 3 patients who were treated with trastuzumab but did not receive treatment with BKM120.

1.2.2.1.2 Human pharmacokinetic and metabolism data

Preliminary clinical pharmacokinetic data of BKM120 after single and multiple daily dosing is available from the first-in-human trial [CBKM120X2101]. BKM120 was administered as a capsule (doses ranging between 12.5 and 150 mg) and full pharmacokinetic profiles were collected on Day 1, Day 8 and Day 28 of Cycle 1.

BKM120 was rapidly absorbed, with the median time to reach the peak plasma concentration (Tmax) ranging from 1.0 to 1.75 hours following administration. Tmax was independent of dose and was not altered after multiple oral doses. Variability in systemic drug exposure was

moderate at all dose levels. At 100 mg the variability in systemic drug exposure and Cmax (CV %) at steady-state was moderate, about 36% and 25%, respectively.

During once daily dosing, plasma BKM120 concentrations were found to accumulate in reaching steady-state. After one week of oral daily dosing (day 8), both Cmax and AUC0-24h were approximately 3-fold higher than after a single dose (day 1). The mean accumulation ratio (Racc) of BKM120 at 100 mg was 2.7 and 3.3 on days 8 and 28, respectively, indicating the absence of significant drug accumulation after day 8.

The decay in BKM120 plasma concentration over time was bi-exponential, with an apparent long terminal half-life. The mean T1/2,acc (effective half-life, obtained from drug accumulation) calculated from exposure data at day 28 ranged between 38 and 49 hours across all dose levels. T1/2,acc was found to be independent of dose. Based on the effective half-life, steady state BKM120 plasma levels can be expected to be reached after 1 week of daily dosing.

Furthermore the preliminary PK data within the Japanese population [CBKM120X1101] show no significant differences in Cmax or AUC0-24h with the Caucasian population [CBKM120X2101]. A preliminary population PK analysis, including data from studies [CBKM120X2101] and [CBKM120X1101] confirmed those findings (Novartis internal data).

In study [CBKM120B2101], BKM120 was administered with GSK1120212 (a MEK inhibitor). Single dose pharmacokinetics of BKM120 appeared to be unaffected by concomitant administration of GSK1120212. Concurrent chronic daily administration of both drugs, however, consistently resulted in a dose- and time-dependent decrease in BKM120 systemic drug exposure. After 28 days of once daily combination treatment of BKM120 with GSK1120212 (1.5-2.0 mg), exposure of BKM120 at system steady-state was decreased by approximately 45-50%, when compared to the mean value determined from [CBKM120X2101]. Decrease in exposure was less pronounced at lower doses of GSK1120212 (0.5- 1 mg) (approximately 25%). The overall drug clearance of BKM120 increased up to 2-fold in the presence GSK1120212. This dose and time dependent effect of GSK1120212 on BKM120 oral clearance is most likely explained by induction of CYP3A4, a property of GSK1120212, which has been demonstrated *in vitro*. These findings are also consistent with a high dependence of BKM120 clearance on CYP3A4 activity. Similar changes in the pharmacokinetics of BKM120 could be expected to occur when other inducers of CYP3A4 are combined with BKM120 treatment (see concomitant medication). The pharmacokinetics of GSK1120212 was not altered by BKM120.

In study [CBKM120X2107] a daily dosing regimen of BKM120 was tested in combination with weekly infusions of trastuzumab in patients with relapsed HER2-overexpressing breast cancer. Preliminary pharmacokinetic data indicated that the systemic drug exposure (Cmax and AUC) of oral BKM120 in combination with trastuzumab was similar to the single agent data. Trastuzumab trough levels were consistent with those previously reported to be therapeutic (i.e., generally greater than 20 μg/ml).

1.2.2.1.3 Clinical efficacy data

Sixty six patients were evaluable for response in study [CBKM120X2101] where all patients in the expansion cohort were required to have mutated and/or amplified PIK3CA and/or mutated PTEN or null/low PTEN protein expression: partial tumor responses (PR) were observed in 3

patients, one of which was a RECIST v1.0 confirmed PR in a patient with triple negative breast cancer and the other 2 not confirmed (1 patient with metastatic breast cancer and 1 patient with parotid carcinoma) (Graña 2011).

The first patient was a 61 year-old female with poorly differentiated ductal metastatic breast cancer assessed as triple negative (ER-, PgR-, HER2-), PI3KCA wild type, PTEN IHC positive. Since 2006 she received many previous anticancer agents (cyclophosphamide, doxorubicin, gemcitabine, docetaxel, paclitaxel, vinorelbine, capecitabine, etoposide, anastrazole). As progressive disease developed (bulky lymph node involvement and local breast relapse), she was enrolled (April 2009) in the Phase I study of BKM120 in the 100 mg/day cohort. A metabolic response (61% decrease in SUV) was observed after 2 cycles, followed by a RECIST partial response (66% tumor shrinkage) after 4 cycles. This patient continues to receive treatment beyond 32 cycles.

The second patient was a 52 year-old female with moderately differentiated ductal metastatic breast cancer, assessed as ER positive, HER2 negative, PI3KCA mutated (E545K & H1047Y), PTEN IHC positive. She had been previously treated with several antineoplastic agents. When she received BKM120 at 100 mg/day (January 2010), she had measurable metastases in the brain, lung and liver. At the second radiological assessment after receiving 4 cycles of BKM120 treatment, a 45% reduction of the sum of the lesions was recorded. The TTP for this patient was 24 weeks.

The third patient was a 45 year-old man with grade 4 parotid gland ductal carcinoma, PI3KCA wild type, PTEN IHC positive. He had been previously treated with doxorubicin and adriamycin. After disease progression was observed on this regimen he was enrolled in the 100mg/day cohort (July 2010) in the [CBKM120X2101] study. At the first radiological assessment after receiving 2 cycles of BKM120 treatment, a 33% reduction of the sum of the lesions was recorded. The TTP for this patient was 16 weeks.

As of the data cut-off, July, 4, 2011, preliminary analysis shows forty-five percent of patients (30 of 66 evaluable) had stable disease as best response, with 20 patients (30%) with a disease stabilization of 3 months or longer. A trend towards better activity (long-term stabilizations) has been observed at the higher dose cohorts, also expressed in metabolic FDG-PET response. However, considering the impact of a PI3K inhibitor on glucose metabolism, further data needs to be acquired to understand whether the current FDG-PET assessment data can be used as a predictive factor for efficacy.

With regards to pharmacodynamic markers observed in study [CBKM120X2101], down regulation of pS6 in skin by 30-80% was demonstrated in 28 out of the 38 evaluable patients at 100 and 150 mg/d and more than 25% FDG-PET signal decrease in patients at doses greater than the MTD.

With regards to the PI3K pathway activation, two of the three responders described above, one had a tumor with the PIK3CA mutation. Moreover, 18 patients had a stable disease lasting for 16 weeks or longer, including 8 patients who had tumors with an activated PI3K pathway. These data are promising and continued exploration of the activity of BKM120 in patients with activated PI3K pathway is warranted.
More specifically, in [CBKM120X2101], 25.3% (21/83) of patients had metastatic breast cancer. At the cut-off date, July, 4, 2011, twenty breast cancer patients were evaluable for

objective tumor response by RECIST 1.0. Two breast cancer patients (11%), described above exhibited partial responses. For these 2 patients, the treatment duration was 27+ (ongoing) and 5 months, respectively. An additional 8 breast cancer patients (40%) had stable disease. Median progression-free survival was 60 days and the 6-month PFS rate was 33% (Rodon 2011).

Please refer to the Investigator's Brochure for additional information on the available clinical experience with BKM120.

1.3 Study Rationale

Thymic tumors are rare tumors, but represent the most common tumors of the anterior mediastinum. Thymoma has an indolent course in advanced disease and has the propensity to spread to the pleura. In disseminated disease, thymoma has demonstrated sensitivity to a broad range of chemotherapeutic agents. In first line therapy, combination chemotherapy produces responses in approximately 80% of patients. A number of single agents have activity in recurrent disease, but none are curable. Patients with recurrent thymoma have limited treatment options, and thus novel target modalities are needed.

At the Indiana University Simon Cancer Center (IUSCC), more patients with advance thymoma are seen than any other institution in the country. We have conducted numerous trials in advanced disease either at the IUSCC or in collaboration with other institutions or national Cooperative Groups. This has permitted us to collect tissue and develop a tumor model and the only existing cell line in this disease. Using our collected thymoma tissues, we have conducted next generation RNA sequencing of thymomas across various histologic types. From this analysis, we identified a unique microRNA cluster on chromosome 19 (C19MC) that is highly overexpressed in a significant subset of thymomas primarily comprised of the A & A/B subtype.

We subsequently validated this observation in additional 35 thymomas by qPCR (Figure 1-2). This cluster is normally silent in adult tissues, with normal expression restricted to embryonic development. MicroRNAs within the C19MC cluster, miR-517 & miR-519d, have been previously demonstrated to inhibit key proteins in the PI3K/AKT pathway. Namely, PTEN, a negative regulator of AKT, and p21, a cell cycle arrest protein (Fornari, et al 2012).

Figure 1-2

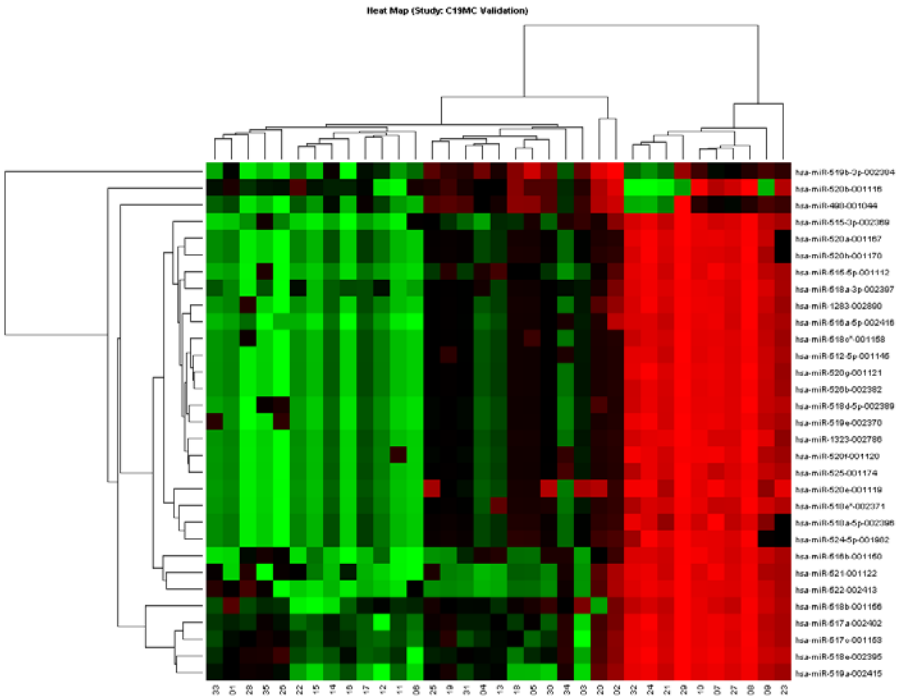


Figure 1-2 RNA-sequencing identified extensive over-expression of the C19MC cluster in A&A/B thymomas in a test set of 13 samples. In this figure we validate the over-expression of the C19MC cluster using qPCR in an independent sample set of 35 thymomas. Expression data demonstrates a separation of the samples into 2 distinct groups as demonstrated by the upper dendrogram. Red represents high-expression, green represents low or no expression. All A & A/B samples were in the C19MC positive group (right-fork of the dendrogram), whereas the B1, B2, & B3 samples were in the C19MC negative group (left-fork of the dendrogram), except for one discordant B1 sample in the C19MC positive group.

In addition, gene expression analysis reveals over-expression of PIK3CA (aka PI3K p110), the canonical activator of AKT (Figure 1-3). To confirm, we performed a quantitative ELISA on a validation set of 35 thymomas for phospho-AKT (Ser 473), and demonstrate that C19MC positive thymomas have significantly higher levels of phospho-AKT compared to C19MC negative thymomas which in-turn has higher levels than adjacent normal tissue (Figure 1-4).

Figure 1-3

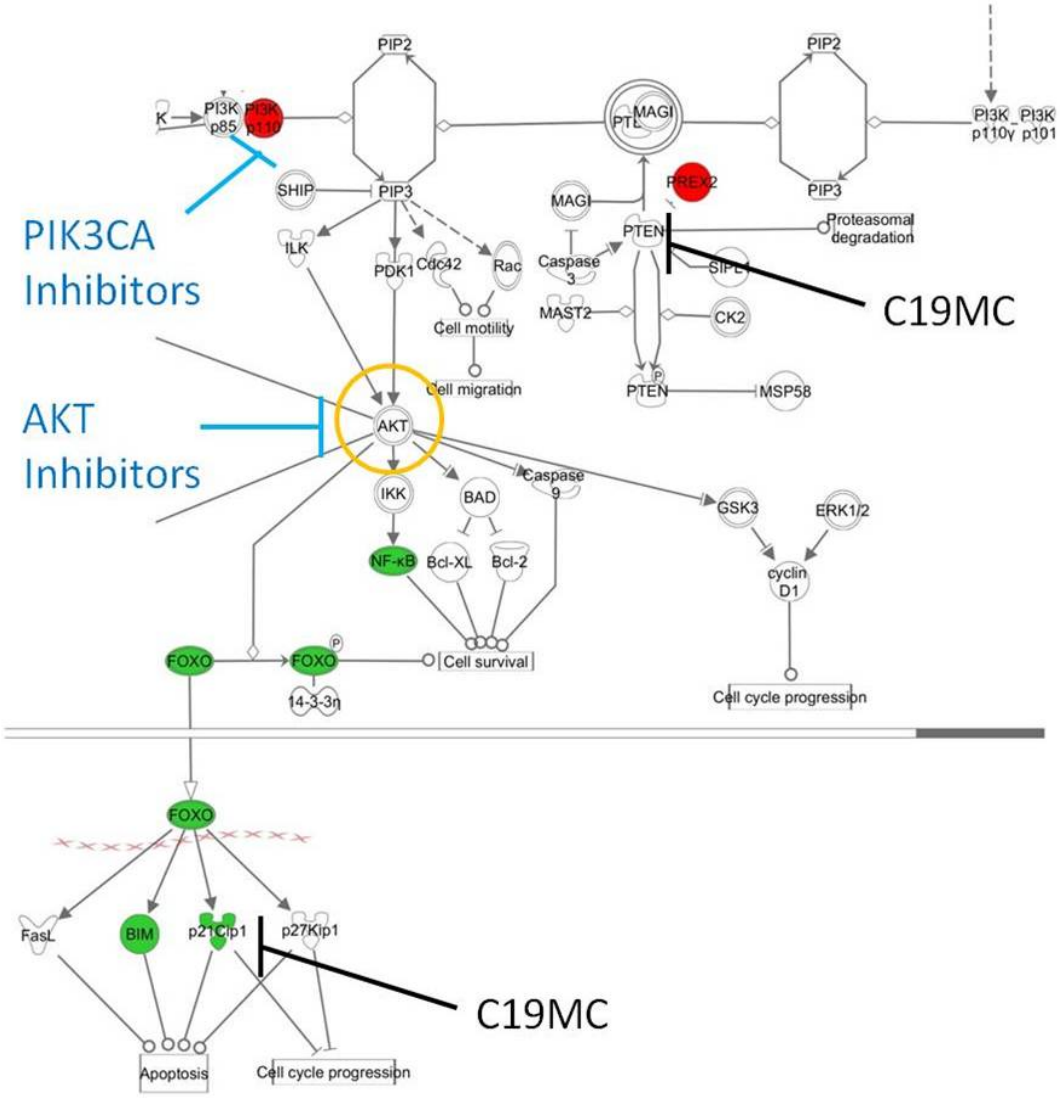


Figure 1-3. Network analysis of thymoma RNA-seq data demonstrates over-expressed genes (RED) and under-expressed genes (GREEN) in C19MC positive thymomas that would be expected of an over-activated PI3K pathway.

Figure 1-4

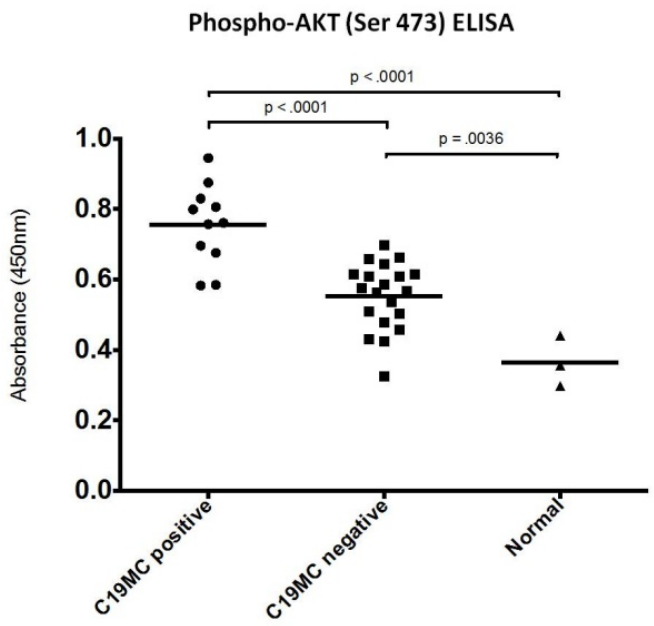


Figure 1-4. Protein ELISA for activated phospho-AKT (Ser 473) in a validation set of 35 thymomas and 3 normal tissues, demonstrating significantly higher phospho-AKT in C19MC positive thymomas vs. C19MC negative vs. normal tissues.

These data demonstrate that all thymomas have the potential to have sensitivity to PI3K inhibition, in particular those that are positive for C19MC. We further tested a variety of PI3K, AKT, and mTOR inhibitors in our thymoma cell line (IU-TAB-1) and found significant activity for several of these agents including BEZ235 and BKM120 (Figure 1-5).

Our main hypothesis is the PI3K pathway is an important driver for growth and metastasis of thymoma and that inhibition of the PI3K pathway is expected to produce clinically meaningful response in patients with recurrent thymoma. Our rationale is to use BKM120, a pan-PI3K inhibitor, which has shown significant cell growth inhibition in thymoma, in a Phase II clinical trial to demonstrate clinical efficacy of this agent in recurrent disease.

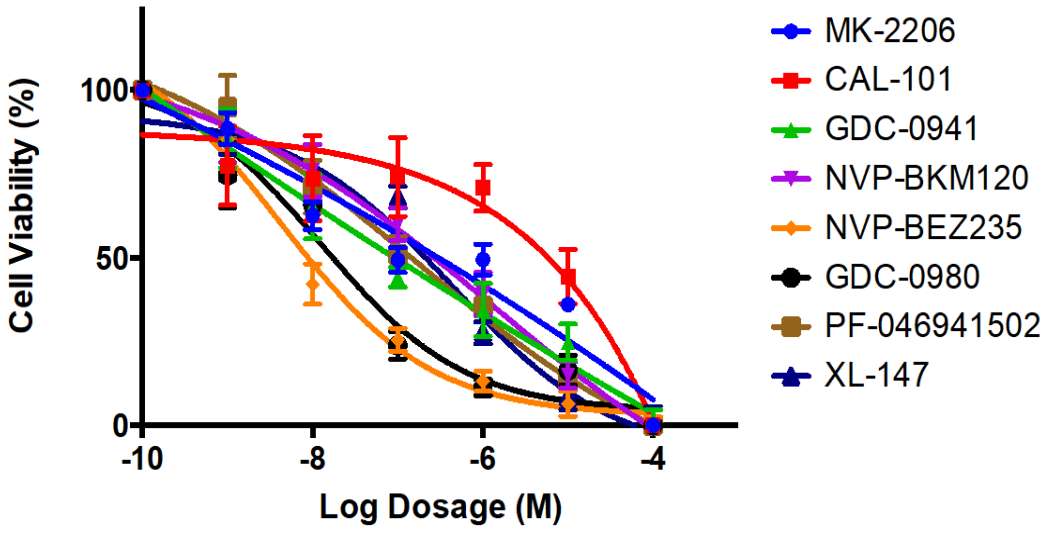


Figure 1-5. The thymoma cell line, IU-TAB-1, tested with increasing doses of PI3K, AKT, and dual PI3K/mTOR inhibitors. Cells were treated for 72 hours and cell viability assessed. The data demonstrates marked sensitivity of the thymoma cell line to these inhibitors

2 Study Objectives

Primary

- To evaluate the objective response rate (CR+PR) in patients with thymomas treated with BKM120.

Secondary

- To evaluate toxicity in patients with thymomas treated with BKM120.
- To evaluate progression-free survival in patients with thymomas treated with BKM120.
- To evaluate disease control rate (DCR = CR+PR+SD) in patients with thymomas treated with BKM120.
- To evaluate duration of response of patients with thymomas treated with BKM120.
- To evaluate overall survival of patients with thymomas treated with BKM120.

Exploratory

- To determine if there are molecular markers to predict response in patients with thymomas treated with BKM120.

3 Exploratory Investigational plan

3.0 Overall Study Design

- **Purpose:** This will be a single arm phase II trial in patients with recurrent thymoma. The purpose of the study is to determine the activity of the pan PI3K Inhibitor, BKM120 in patients with this disease.

- **Planned treatments:** BKM120, 100 mg capsule for oral use, taken once daily for two or more months for a maximum of one year. Each cycle is 28 days.

- **Sequence & duration of study periods:** Eligible patients will be treated for two months and evaluated. All patients with responding or stable disease will continue on study unless there is unacceptable toxicity or progression of disease. Patients will continue on study for a maximum of one year or until progression. There will be no dose escalations.

- **Blinding:** Open Label.
- **Structure:** Single Group.
- **Randomization:** Non-randomized.
- **Placebo Controlled:** No
- **Number of Patients & Centers:**
  - 25 thymoma patients (16 in stage 1 + 9 in stage 2)
  - Because some patients may not be evaluable for response, up to 27 patients may be accrued to ensure that the number of evaluable patients is 25.
  - Number of Centers: IUSCC, other centers may be added with approval of the sponsor (e.g. Georgetown, Stanford, Memorial Sloan-Kettering and MD Anderson).

3.1 Study Population

3.1.1 Patient Population

A total of 27 eligible patients with recurrent thymoma who will meet the eligibility criteria will be enrolled for this trial. The patients will be enrolled in two stages. 16 eligible patients will be enrolled for stage 1 and if at least 2 thymoma patients have response to treatment then the study will continue for stage 2 where an additional 9 eligible patients will be enrolled. Because some patients may not be evaluable for response, up to 27 patients may be accrued to ensure that the number goal of evaluable patients is met.

3.1.2 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, which assure 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:

3.1.2.1 Inclusion Criteria

1. Histological confirmation of thymoma.
2. At least one prior line of platin-based chemotherapy (unless refused or not tolerated).
3. Documented progressive (clinical and/or objective) disease after the most recent systemic therapy regimen.
4. Patients must not have received chemotherapy, radiation therapy, or undergone major surgery within 4 weeks prior to enrollment.
5. Patient must not have other curative treatment options (e.g. surgical resection of solitary metastases if feasible, or other proved curative options if they become available in the future).
6. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for nonnodal lesions and short axis for nodal lesions) as >20 mm with conventional techniques or as >10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 4 for the evaluation of measurable disease.
7. Age ≥ 18 years
8. ECOG performance status ≤ 2
9. Patient must be able to swallow and retain oral medications
10. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 109/L, Platelets ≥ 100 x 109/L, Hb >9 g/dL

11. Total calcium (corrected for serum albumin) within normal limits (biphosphonate use for malignant hypercalcemia control is not allowed)
12. Magnesium ≥ the lower limit of normal
13. Potassium within normal limits for the institution
14. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal range (or ≤ 3.0 x upper limit of normal (ULN) if liver metastases are present)
15. Serum bilirubin within normal range (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)
16. Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
17. Serum amylase ≤ ULN
18. Serum lipase ≤ ULN
19. Fasting plasma glucose ≤ 120 mg/dL (6.7 mmol/L)
20. HbA1c ≤ 8 %
21. Negative serum pregnancy test within 72 hours before starting study treatment in women with childbearing potential
22. Signed informed consent
23. INR ≤ 2

3.1.2.2 Exclusion Criteria

Patients eligible for enrollment into the treatment phase of this study **must not meet any** of the following criteria:

1. Patients who have received prior treatment with a P13K inhibitor.
2. Patients with thymic carcinoma (formerly WHO Type C).
3. Patients with a known hypersensitivity to BKM120 or to its excipients
4. 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), is clinically stable at the time of study entry and is receiving low dosage corticosteroid therapy
5. Patients with acute or chronic liver, renal disease or pancreatitis
6. Patient has acute viral hepatitis or a history of chronic or active Hepatitis B (HBV) or Hepatitis C (HCV) infection, (typically defined by elevated AST/ALT (persistent or intermittent), high HBV DNA level, HBsAg positive, or high HCV RNA level (testing not mandatory, refer to Section 4.6.6.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up).
7. Patients with the following mood disorders as judged by the Investigator or a psychiatrist, or as a result of patient's mood assessment questionnaire:
    - 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) or patients with active severe personality disorders (defined according to DSM- IV) are not eligible**.** Patients with mild depressive or

anxiety disorders who are stable at the time of enrollment and on antidepressants not listed in Tables 4-0 and 4-1 of the study protocol will be permitted to enroll on this study. **Note: for patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.**

- ≥ CTCAE grade 3 anxiety
- Meets the cut-off score of ≥ 12 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)

8. Patients with diarrhea ≥ CTCAE grade 2
9. Patient has known active cardiac disease including any of the following:
    - Left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Grated acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc > 480 msec on screening ECG (using the QTcF formula)
    - Angina pectoris that requires the use of anti-anginal medication
    - Ventricular arrhythmias except for benign premature ventricular contractions
    - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
    - Conduction abnormality requiring a pacemaker
    - Valvular disease with document compromise in cardiac function
    - Symptomatic pericarditis
10. Patient has a history of cardiac dysfunction including any of the following:
    - Myocardial infraction within the last 6 months, documented by persistent elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LVEF function
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
11. Patient has poorly controlled diabetes mellitus or steroid-induced diabetes mellitus
12. Patients with chronic lung disease, dyspnea at rest, or interstitial lung disease
13. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection; uncontrolled hypertension, i.e. BP >160/100) 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, O_2 saturation at rest on room air should be considered to exclude pneumonitis or pulmonary infiltrates.
14. 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

15. 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
16. 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 4-1 or a list of prohibited QT prolonging drugs with risk of Torsades de Pointes.
17. 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. intra-articular) are allowed. Patients with previously treated brain metastases, who are on stable low dose corticosteriod treatment (e,g dexamethasone 2 mg/day, predisolone 10 mg/day) for at least 14 days before start of study treatment are eligible.
18. 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, pummelos, or exotic citrus fruits.
19. 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 4-0 for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).
20. Patients who have received chemotherapy or targeted anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, antibodies or mitomycin-C) prior to starting study drug must recover to a grade 1 before starting the trial
21. 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
22. Patients who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
23. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
24. Patients who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant.
25. 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 potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must 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 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 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 condoms during treatment, for 4 weeks (5 T1/2) after stopping treatment and for an 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.

26. Known diagnosis of human immunodeficiency virus (HIV) infection
27. History of another malignancy within 3 years, except cured basal cell carcinoma of the skin or excised carcinoma in situ of the cervix
28. Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

4 Treatments

4.0 BKM120 Administration

The study drug BKM120 will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. BKM120 will be administered on a continuous once daily dosing schedule. Patients should be instructed to take the dose of BKM120 daily in the morning, one hour after a light breakfast (morning meal) at approximately the same time each day. 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 them. Do not crush capsule. Patients should continue to fast for 2 hours after the administration of each BKM120 dose.

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, , 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 dose AFTER 6:00 PM, then the dose should be withheld that day and BKM120 should be restarted the following day.

Patients must avoid consumption of St. John's Wort, Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, pummelos 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 BKM120 dose delay of >28 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.

4.1 Concomitant Therapy

All medications (excluding prior chemotherapy and biologic, immunologic or radiation therapy) taken within 4 weeks prior to the administration of 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 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 4.0.2.1.

4.1.1 Drugs that are Prohibited

- Other investigational therapies must not be used while the patient is on the study.
- Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) 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 4-0 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 4-0 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 4-1 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), ginko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginsing. 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.

Table 4-0 List of prohibited CYP3A Inhibitors and Inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	aprepitant	avasimibe	bosentan
conivaptan	atazanavir	carbamazepine	efavirenz
grapefruit juice	cimetidine	Phenobarbital (barbiturates)	etravirine
indinavir	ciprofloxacin	phenytoin	modafenil
itraconazole	darunavir	rifabutin	nafcillin
ketoconazole	diltiazem	rifampin	ritonavir
lopinavir	erythromycin	St. John's Wort	talviraline
mibefradil	fluconazole		tipranavir
nefazodone	tofisopam		
nelfinavir	verapamil		
posaconazole	amprenavir		
ritonavir	fosamprenavir		
saquinavir	elvitegravir		
telithromycin	tipranavir		
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 4-1 List of prohibited QT prolonging drugs

All QT-prolonging drugs listed in Table 4-1 are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 4-3 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

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 U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	

Drug	QT risk(*)	Comment
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
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	
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
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 sibstrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 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.

4.1.2 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 4-2 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.
- If a patient, after study enrollment, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for torsade de pointes then the investigators, at their discretion, may co-administer such medications. Patients receiving such medications must be monitored. Refer to Table 4-3 for a list of QT prolonging medications to be used with caution.

  Note: please refer also to Table 4-1 for a list of **prohibited** QT prolonging medication.
- Please refer to Table 4-2for a list of CYP450 substrates and carefully consider their co-administration with BKM120.
- Concomitant treatment with corticosteroids and BKM120 should be avoided, whenever possible, during this study. 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.

Table 4-2 List of CYP450 substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	Adinazolam	felodipine[1]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	fentanyl[2]
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	flunitrazepam

repaglinide	fluvastatin	clomipramine	Alprazolam	fluticasone[1]
rosiglitazone	glibenclamide (glyburide)	clopidogrel	Amlodipine	lovastatin[1]
torasemide	gliclazide	diazepam	Aripiprazole	maraviroc[1]
troglitazone	glimepiride	fluoxetine	Atorvastatin	midazolam[1]
	glipizide	imipramine	Brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam[1]	nisoldipine
	irbesartan	mephobarbital	budesonide[1]	nitrendipine
	ketobemidone	moclobemide	buspirone[1]	perospirone[1]
	lornoxicam	omeprazole	Capravirine	quinine
	losartan	pantoprazole	Cerivastatin	sildenafil[1]
	meloxicam	progesterone	Chlorpheniramine	simvastatin[1]
	naproxen	quazepam	cyclosporine[2]	sirolimus[1,2]
	nateglinide	rabeprazole	darifenacin[1]	tolvaptan
	piroxicam	sertraline	Diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine[2]	triazolam[1]
	S-ibuprofen		ebastine[1]	
	sulfamethoxazole		eletriptan[1]	
	tenoxicam		eplerenone[1]	
	tolbutamide		ergotamine[2]	
	torasemide		Estazolam	
	valdecoxib		everolimus[1]	

* 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).

Table 4-3 List of QT prolonging drugs to be used with caution

Drug	QT risk	Comment
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	

Drug	QT risk	Comment
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	*not available in the United States
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	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

4.2 Interruption or Discontinuation of Treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of BKM120 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 4-4. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0. Patients requiring dose reduction due to toxicity will not be dose re-escalated following resolution of the toxicity.

(CTCAEv4.0,

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf).

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

Table 4-4 BKM120 dose level modification guidelines

Dose level	Dose and schedule
-2	**60 mg daily**
-1	**80 mg daily**
*** 0**	**100 mg daily**

* Starting Dose

Table 4-5 Criteria for interruption and re-initiation of BKM120 treatment

Recommended dose modifications and criteria for treatment interruption and re-initiation with treatment-related adverse events

These changes must be recorded on the Dosage Administration Record CRF

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) **Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)**	**Maintain dose level**
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) **Grade 4 (ANC < 0.5 x 10^9/L)**	**Omit dose until resolved to ≤ Grade 1, then:** **If resolved in ≤ 7 days, then maintain dose level** **If resolved in > 7 days, then ↓ 1 dose level**
Febrile neutropenia **(ANC < 1.0 x 10^9/L, with a** single **temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)**	**Omit dose until resolved, then ↓ 1 dose level**
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 dose until resolved to ≤ Grade 1, then:** **If resolved in ≤ 7 days, then maintain dose level** **If resolved in > 7 days, then ↓ 1 dose level**
Grade 4 (PLT < 25 x 10^9/L)	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**
RENAL	
Serum creatinine	
Grade 1 (< 2 x ULN)	**Maintain dose level**
Grade 2 (2 – 3 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 ↓ 1 dose level**
Grade 3 (> 3.0 – 6.0 x ULN)	**Permanently discontinue patient from BKM120**
Grade 4 (> 6.0 x ULN)	**Permanently discontinue patient from BKM120**
HEPATIC	
Bilirubin **(*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)** **will be fractionated if elevated**	
Grade 1 (> ULN - 1.5 x ULN)	**Maintain dose level with LFTs* monitored as per protocol**

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 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 ↓ 1 dose level**
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	**Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from BKM120**
Grade 4 (> 10.0 x ULN)	**Permanently discontinue patient from BKM120**
AST or ALT	
AST or ALT without bilirubin elevation > 2ULN Note: confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
Same grade as baseline (i.e., Grade 0 or 1 [> ULN – 3.0 x ULN] if presence of liver metastasis	**Maintain dose level with LFTs* monitored per protocol**
Increase from baseline Grade 0 to > 1.5 ULN or from baseline Grade 1 to Grade 2	**Can continue treatment at ↓ 1 dose level**
Increase of two grades from baseline (from baseline Grade 0 to Grade 2 or from baseline Grade 1 to Grade 3)	**Omit dose until resolved to Grade 1 or less, then ® 1 dose level** **If no recovery in ≤ 28 days, discontinue permanently BKM120**
Grade 4 (> 20.0 x ULN)	**Discontinue BKM120 permanently**
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	**Permanently discontinue BKM120*** **
***(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) ** In case of recurring Grade 3 or higher toxicity after re-challenge, patients should be permanently discontinued *** All patients with ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN in the absence of cholestasis ULN must immediately be withdrawn from BKM120 and every attempt should be made to carry out the liver event follow-up assessments as described below in Section 4.4.5.2 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) and Section 4.6.6.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up).** Hepatic toxicity 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):** 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 or bilirubin* values** Cycle 3 and onward: monthly **or more frequently if clinically indicated** **In case of any occurrence of ALT/AST or 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 or bilirubin* increase ≥** grade 3 **the liver function tests must be monitored** weekly **or more frequently if clinically indicated** until resolved to ≤ grade 1**; hereafter 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).**	
ENDOCRINE/METABOLIC	
Fasting Plasma Glucose (FPG)	

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
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 according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study** **● consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications),** **● check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks**
Grade 2 (>160 - 250 mg/dL) (> 8.9 - 13.9 mmol/L)	**● If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), manage as for Grade 3 hyperglycemia (see below)** **● If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2:** **○ maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1** **○ initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if not improvement after several days.** **○ instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study** **○ if FPG does not resolve to ≤ Grade 1 within 14 days after institution of appropriate anti-diabetic treatment reduce BKM120 by 1 dose level** **● Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks**
Grade 3 (> 250 - 500 mg/dL) (> 13.9 - 27.8 mmol/L)	**Omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 3:** **● administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate** **● continue to omit BKM120** **● monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1** **● If FPG resolves to ≤ Grade 1 in 7 days or less, then re-start BKM120 and ↓ 1 dose level** **● If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from BKM120**

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
	● initiate or continue anti-diabetic treatment as appropriate ○ instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ○ consider use of oral anti-hyperglycemic therapy such as metformin ● check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit BKM120 and following guidance for management of Grade 3 fasting plasma glucose (FPG)
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 grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4: ● administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate ● discontinue patient from BKM120 ● instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ● consider use of oral anti-hyperglycemic therapy such as metformin ● check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue BKM120 and following guidance for management of Grade 4 fasting plasma glucose (FPG).**
CARDIAC	
Cardiac - Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	**Maintain dose level, and continue BKM120 with caution Repeat LVEF within 4 weeks or as clinically appropriate**
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	**● Omit BKM120 until resolved* (as defined below), then ↓ 1 dose level ● LVEF measurement to be repeated, if not resolved* within 21 days, permanently discontinue patient from BKM120 treatment**
Refractory or poorly controlled, ejection fraction < 20%	**● Permanently discontinue patient from BKM120**
***the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.**	
Cardiac – QTc prolongation	

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	**First Occurrence:** ● **omit BKM120** ● **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 or >60ms from baseline** ● **If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input.** ● **Once QTcF prolongation has resolved, BKM120 may be restarted at a one lower dose level** **Second Occurrence:** ● **Permanently discontinue patient from BKM120**
Other Cardiac Events	
Grade 1 or 2	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**
Grade 4	**Permanently discontinue patient from BKM120**
OTHER	
Mood alteration/Psychiatric Disorders	
*** Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.**	
Grade 1*	● **Maintain dose level** ● **Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)**
Grade 2*	● **Omit dose until resolved to ≤ Grade 1 or baseline status** ● **Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)** ● **First event: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then maintain the dose level** ● **Second and further events: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then ↓ 1 dose level**
Grade 3*	**Omit dose until resolved to ≤ Grade 1 or baseline status** ● **Psychiatric consultation is required and introduce optimal management** ● **if the condition resolved to Grade ≤1 or to baseline status, continue to co-medicate and then ↓ 1 dose level**
Grade 4*	**Permanently discontinue patient from BKM120** ● **Psychiatric consultation is required** ● **Introduce optimal management (e.g. as per local guidelines)**
Rash	
Grade 1	**Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)**
Grade 2	**First occurrence: Omit dose until resolved to grade ≤ 1 then:** ● **If resolved in ≤ 2 weeks, maintain dose level.** ● **If resolved in more than 2 weeks, ↓ 1 dose level.** **Second occurrence: ↓ 1 dose level.** **Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)**

Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
Grade 3	**First occurrence: omit dose until resolved to CTCAE Grade ≤ 1; then ↓ 1 dose level.** **Second occurrence: permanently discontinue patient from BKM120.** **Consider referral to dermatologist and manage rash per dermatologist's recommendation.** **According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.**
Grade 4	**Permanently discontinue patient from BKM120.** **Consider referral to dermatologist and manage rash per dermatologist's recommendation.** **According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.**
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, ↓ 1 dose level**
Pneumonitis	please see Table 4-8, Section 4.1.2.4.1 for additional follow up for selected toxicities
Other non- hematological adverse events	
Grade 1 or 2	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**
Grade 4	**Permanently discontinue patient from BKM120** *Note:* **Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic**
Mucositis	
Grade 1 / Tolerable Grade 2	**Maintain dose level.** **Non-alcoholic or salt water mouth wash (see also section for additional follow up for selected toxicities)**
Intolerable Grade 2 or Grade 3	**First occurrence: hold until resolved to grade ≤ G1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator).** **Second occurrence: hold until resolved to grade ≤ G1 and ↓ 1 dose level.**
Grade 4	**Permanently discontinue patient from BKM120.**
**** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.** **These changes must be recorded on the Dosage Administration Record eCRF.**	

4.3 Monitoring of BKM120 Suspected Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event, clinically significant laboratory value(s) or abnormal test procedure result(s), must be followed as outlined in Table 4-5, 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 > 28 days from the intended day of the next scheduled dose and has had more than two dose reductions, 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 (i.e., patients cannot be treated below dose level -2). All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of BKM120. All SAEs must be reported to Novartis as detailed in section 4.2.5.1

4.4 Known Undesirable Side Effects of BKM120

4.4.1 Neuropsychiatric Events

In an ongoing Phase Ia study of BKM120 in patients with solid tumors (CBKM120X2101), neuro-psychiatric adverse events, including reversible and generally mild to moderate mood alterations, described as anxiety, agitation with crying episodes and depression have been reported in patients treated with BKM120. In this study, three out of five patients with moderate to severe mood alterations had a history of depression and/or anxiety. All patients with a documented medical history of depression/anxiety also developed mood alterations while treated with BKM120 at the 100 mg dose level and thus reflecting a potential risk group of patients.

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. Patients with corresponding symptoms CTCAEhy Grade ≥ 2 should immediately be examined by a psychiatrist and closely followed medically. 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 a psychiatrist.

4.4.1.1 Management of Mood Alteration

Guidelines for the treatment of BKM120 induced psychiatric disorders

Psychiatric adverse events will be closely monitored and evaluated at each planned visit until recovery to Grade ≤ 1 or baseline status. The grading of psychiatric adverse events/mood alterations must be based on the clinical interpretation of severity according to the NCI- CTCAE (v 4.03) guidelines.

For patients who experience new or worsening of existing psychiatric AEs of Grade ≥1, psychiatric consultation should be considered as described in Table 4-5.

Patient self-reported mood questionnaires (GAD-7 and PHQ-9) will be used for screening and during the study treatment phase to aid the investigator in identifying new or worsening of events. For additional information regarding safety assessments based on patient self-reported mood questionnaires, please refer to Section Patient self-rating mood questionnaires.

If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit treatment with BKM120 and refer the patient to the on-site psychiatrist

or a local psychiatrist for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment. During the study, subjects will be monitored at regular scheduled visits (eg, Day 15 of Cycle 1, Day 1 and Day 15 of Cycles 2, Day 1 of each subsequent cycle, and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self-reported questionnaires. For patients who fax or email their questionnaires; the study nurse will promptly review the questionnaires as they become available. Additional assessments may be done according to the clinical judgment of the investigator if desired.

Table 4-6 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 _____

Table 4-7 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 _____

4.4.2 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, without clear influence of the dose or the time point of testing. Histopathologically, pancreas and liver showed changes which are in concordance with this activity.

Grade 4 Hyperglycemia was also observed in an ongoing Phase Ia 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 4-5.

4.4.2.1 Management of Hyperglycemia

In addition to the dose modification and hyperglycemia treatment guidelines in Table 4-5:

- Under the supervision of an endocrinologist, an insulin regimen should be initiated according to institutional standard of care or the Treat-To-Target Algorithm for Lantus® (Riddle, Rosenstock, and Gerich 2003).

• For any hyperglycemia ≥ grade 1, the patient should continue to follow dietary guidelines provided by the American Diabetes Association (American Diabetes Association 2004).

• 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.

• 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.

• 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.

4.4.3 Cardiac Events

Cardiac safety studies, conducted in vitro and in vivo, did not indicate a prominent electrophysiological risk. The only effect considered relevant was a trend towards an increase in 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 or unstable cardiac disease or cardiac disease requiring continuous treatment, and no patients with uncontrolled hypertension will be enrolled in early clinical studies. In addition, all patients will be assessed for cardiac diseases before start of treatment, while all patients enrolled in the trial will undergo regular

cardiac monitoring throughout the conduct of the trial. For the treatment of acute cardiac events occurring under BKM120 treatment investigators are advised to adhere to the protocol guidelines. Vital signs, including pulse rate and blood pressure, will closely be followed during the early clinical studies.

4.4.3.1 Management of Cardiac Events

At the screening visit a 12-lead electrocardiogram (ECG), and an echocardiogram or MUGA (ECHO/MUGA) will be performed to assess eligibility. Repeat ECGs will be performed at screening and as clinically indicated. An ECHO/MUGA will be repeated at Cycle 4 and then every 4th cycle thereafter.

4.4.4 Lung Toxicity/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 pneumonitis grade 2 eight weeks after the first dose of BKM120 at 100 mg 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 patient given 100 mg one month after the start of study medication with BKM120. The patient experienced pneumonitis with fatal outcome which was concomitant to 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).

4.4.4.1 Management of Pneumonitis

All patients participating in clinical trials with BKM120 will be routinely asked about and observed for the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function tests 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, the guidelines (including dose modifications) in Table 4-8 should be followed. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment.

Table 4-8 Management 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, (or as per local practice) 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, DLCO, and room air O_2 saturation at rest. Repeat at least every 8 weeks, (or as per local practice) 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 3) 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 28 days.**
Grade 3	**CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks, (or as per local practice) 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 28 days 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, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks, (or as per local practice) 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.**

4.4.5 Liver Toxicity

4.4.5.1 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 or bilirubin* values.

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

4.4.5.2 Management of **H**epatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN)

Criteria for interruption and re-initiation of BKM120 treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in Section 4.2, Table 4-5. Patients with clinically significant liver test abnormalities should perform liver-directed medical history, physical examination and other tests as medically indicated to assess potential relationship with study treatment and rule out other underlying causes (e.g. disease progression/obstruction, infection/hepatitis or other liver diseases, sepsis, metabolic diseases including diabetes, concomitant medications including herbals, alcohol, drug-drug interaction, cardiovascular disease/ischemia, other organ injuries, etc.). Any pre-existing liver conditions or risk factors should be reported in the respective medical history and concomitant medication CRF pages (if not done already). All patients with ALT or AST >3.0 x ULN and total bilirubin > 2.0 x ULN in the absence of cholestasis (elevation of alkaline phosphatase [ALP] in patients without bone metastasis or if bone metastasis are present elevation of 5'-nucleotidase and ALP liver fraction) must be immediately withdrawn from BKM120, and every attempt should be made to carry out locally the liver event follow-up assessments as described below:

- Inform the sponsor about the event immediately after its occurrence by reporting the event immediately in the clinical database if it meets the criteria for an AE or SAE.

- Evaluate if associated with the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, or other organ involvement.

- Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.

- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease including metastasis or new lesions, obstruction/compression, etc.

- Perform viral hepatitis and other serology tests:
    - Hepatitis C (HCV) serology and viral RNA, Hepatitis B (HBV) serology and viral DNA, Hepatitis A (HAV) Immunoglobulin M (IgM) and HAV total
    - Hepatitis E (HEV) serology: IgM and IgG, viral RNA
    - Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Epstein-Barr viral (EBV) serology

- Verify and record the use of concomitant medications, acetaminophen, herbal remedies, and other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.

- Consultation with a specialist(s) or a hepatologist(s) is recommended.

• Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury

• LFTs should be followed-up weekly until resolve to ≤ grade 1, baseline or stabilization (no CTCAE grade change over 4 weeks) and outcome documented on the respective AE and lab chemistry pages.

4.4.6 Skin Toxicity/Hypersensitivity

Buparlisib should be discontinued in cases of CTCAE grade 3/4 hypersensitivity reaction and medical intervention according to the local standards instituted.

4.5 Study Termination

A patient is considered terminated from the study when the decision to permanently stop the study medication and survival follow-up is made. Subjects can terminate their participation in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled. A subject's participation may be terminated by the Principal Investigator due to any of the following:

1. adverse event(s)
2. protocol violation
3. subject withdrew consent
4. lost to follow-up
5. administrative problems
6. Death
7. If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose and has had more than two dose reductions, then the patient should be discontinued from the study.

The reasons in which a subject is terminated from the study must be documented in the patient's chart or records.

4.6 Visit Schedule and Assessments

4.6.1 Visit Schedule

Table 4-9 Evaluation and Visit Schedule

Examination	Screening/ Baseline	Cycle 1		Cycle 2		Cycle 3- Cycle n[11]									Follow-up
Day of Cycle	**-21**	**1**	**15[8]**	**1**	**15[8]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**etc**	**EOT**	
Informed consent	X														
Medical History	X														
Central Pathology Review[9]	X														
Inclusion/exclusion criteria	X														
Serum Pregnancy Test (within 72 hours of first treatment for WOCBP)	X	**As clinically indicated.**													
Urinalysis	X													X	
Vital signs	X	X	X[8]	X	X[8]	X	X	X	X	X	X	X	X	X	
Genomic Analysis		X[10]													
Physical examination (including skin rash assessment)	X	X		X		X	X	X	X	X	X	X	X	X	
Performance Status ECOG	X	X		X		X	X	X	X	X	X	X	X	X	
Neuro-psychiatric assessment (PH1-9 & GAD-7)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MUGA/ECHO[2]	X						X				X			X	
12-lead ECG	X		X	**As clinically indicated**											
Radiological tumor assessment/response assessment (Chest CT scan)[3]	X					X		X		X		X		X	
Hematology[4]	X	X	X[8]	X	X[8]	X	X	X	X	X	X	X	X	X	
Serum Chemistry[5]	X	X	X[8]	X	X[8]	X	X	X	X	X	X	X	X	X	
Coagulation Profile[6]	X			X			X		X		X		X	X	
Fasting plasma glucose[7]	X	X	X[8]	X	X[8]	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X		X		X	X	X	X	X	X	X	X	X	
Overall Survival															X
Hepatotoxicity follow-up testing procedures	**As clinically indicated**														

[1] PHQ-9 and GAD-7 questionnaires will be completed in clinic at each visit through the end of Cycle 2. Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis On Day 1 starting at Cycle 3 and for all subsequent cycles while active on the treatment portion of the study. Questionnaires on day 15 of cycles 1 and 2, as well as any other questionnaires required at times other than the scheduled visits can be completed by the patient at home and faxed to the Investigator or the authorized study member for evaluation to fax number (317-274-8007) or sent via PDF.

[2] MUGA/ECHO Baseline, Cycle 4 then every 4th cycle.

[3] Radiological tumor assessment should be performed at screening and every 8 weeks from start of treatment until progression of disease as per RECIST 1.1, or end of treatment. All assessments should be performed within ±7 days of the scheduled day of assessment. Other scans, as appropriate for measurements will be performed at the same time interval.

[4] Hematology - WBC plus differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts, hemoglobin and platelets. Should be performed on D1, and D15 of cycle 1 and 2 and day 1 of all subsequent cycles.

[5]Serum chemistry - 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. C1D1 assessments may be performed up to 72 hours prior to the scheduled visit. All other draws should occur within 24 hours of the intended visit.

[6] Coagulation - PT or INR, PTT, and C1D1 assessments may be performed up to 72 hours prior to the scheduled visit. Additional assessments will be performed on Day 1 of Cycle 2 (≤ 72 hours prior to dosing) and repeated every other cycle. A repeat coagulation profile panel is required at the time of study treatment discontinuation. 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.

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

[8] May be performed at outside institution with results transmitted via fax (to fax number 317-274-8007) or via PDF.

[9]Pathology will undergo central review by IU Department of Pathology to confirm eligibility which will include obtaining blocks or primary or metastatic lesion s which can be obtained prior to the 21-day screening window.

[10]Genomic analysis consists of collecting peripheral whole blood prior to the first dose of chemotherapy. DNA and RNA will be extracted from a core tumor specimen as part of standard of care prior to enrollment. See Section 4.2.6, Collection of Genomics Data.

[11] Assessments for Cycles 3 and beyond will occur on Day 1.

4.6.2 Efficacy Assessments

4.6.2.1 Anti-Tumor Effect

Imaging will be obtained at baseline and at the end of every two cycles. Tumor responses will be assessed by Response Evaluation Criteria in Solid Tumors Guideline (RECIST v1.1) (Eisenhauer, et al 2009).

4.6.2.2 Measurement Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1) Measurable:

- Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT, MRI or PET scan (slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray

- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT, MRI or PET scan (slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

2) Non-measurable:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging.

4.6.2.3 Specifications by Methods of Measurements

1) Measurement of Lesions:

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

2) Method of Assessment:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

4.6.2.4 Tumor Response Evaluation

Baseline documentation of 'target' and 'non-target' lesions

- When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

4.6.2.5 Response Criteria

For other details and special circumstances of the RECIST 1.1 guidelines, refer directly to reference.

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Time Point Response of Target Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not Evaluated	No	PR
PR	Non-PD or Not All Evaluated	No	PR
SD	Non-PD or Not All Evaluated	No	SD
Not All Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

4.6.2.6 Definitions of Endpoints

- **Progression-Free Survival (PFS):** Duration of time from start of treatment to time of documented progression or death
- **Overall Response Rate (ORR):** Number of patients who achieve either a partial or complete response divided by the number of patients
- **Duration of Response (DoR) (Among Responders, PR + CR)**: A measurement from the earliest time when response criteria are met until death or progression. Patients still meeting the criteria for response at the end of the study are treated as censored.
- **Overall Survival (OS):** Time from the date of enrollment to the date of death due to any cause or the last date the patient was known to be alive (censored observation) at the date of data cutoff for the final analysis
- **Disease Control Rate (DCR):** Number of patients who achieve either a partial or complete response or stable disease for at least 4 months divided by the number of patients.

4.6.3 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.

These assessments should be performed within ±2 days 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/docs/ctcaev4.pdf.

4.6.4 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.

4.6.5 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 the investigational drug can be found in the [Investigators' Brochure]. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

4.6.5.1 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 (specify what this includes)
  - 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 to Novartis 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.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report in English, and send the completed, signed form by fax (877-778-9739) within 24 hours to the Novartis Drug Safety and Epidemiology Department.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same person 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, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, 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.

4.6.5.2 Novartis Instructions for Rapid Notification of Serious Adverse Events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (877-778-9739**), to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence.** 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.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the 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).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. 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 (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 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.

For details on the most appropriate contraception you may talk to your regular doctor or if 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.

4.6.6 Laboratory Evaluations

4.6.6.1 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: Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered "of non-childbearing potential". This should be documented appropriately in the patient's medical history. Additional pregnancy tests should be performed as clinically indicated.

4.6.6.2 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.

4.6.6.3 Coagulation Profile

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

4.6.6.4 Serum Chemistry

Biochemistry includes the following parameters: 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. C1D1 assessments may be performed up to 72 hours prior to the scheduled visit. All other draws should occur within 24 hours of the intended visit.

Because accurate serum glucose and lipid measurements are required, patients should be fasting at the time of the blood sampling.

4.6.6.5 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.

4.6.6.6 Hepatotoxicity

Hepatotoxicity follow-up testing will be performed when needed (refer to Section 4.4.5.2 Management of hepatotoxicity [ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN]).

4.6.6.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up

Viral hepatitis serologic tests are performed confirm patient's eligibility when needed per clinical judgment and specific patient's clinical circumstances.

During study treatment, viral hepatitis serologic and other tests will be performed as per the guidelines of management of hepatotoxicity (ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN) in patients receiving BKM120. Refer to Section 4.4.5.2 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) for details.

Viral hepatitis serology includes the following:

- Hepatitis A IgM antibody and hepatitis A serology total
- Hepatitis B surface antigen, Hepatitis B Core Antibody (IgM) and viral DNA
- Hepatitis C serology and viral RNA
- Hepatitis D RNA (where needed)
- Hepatitis E IgM and IgG antibody and viral RNA

Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia. Novartis Confidential Page 18 BKM120 liver toxicity standard language based on protocol CBKM120F2303 Amendment 3 Additional viral serology tests may include:

- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Herpes Simplex Virus

Table 4-10 Clinical laboratory parameters collection plan

Test Category	Test Name
Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up *	HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb, ALP, CPK, LDH, WBC (eosinophilia), and others.
* Hepatotoxicity follow-up testing/procedures will be performed locally (refer to Section 4.4.5.2 Management of hepatotoxicity [ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN] and Section 4.6.6.7 Viral hepatitis serology and other tests for hepatotoxicity follow-up).	

4.6.6.8 Collection of Genomics Data

A genomic analysis will be performed and analyzed if there are statistically objective responses to identify markers for patients who respond and do not respond to therapy. For each patient, DNA & RNA will be extracted from a core tumor specimen collected as part of standard of care prior to enrollment. Blocks or 5 (10 micron thick) slides should be requested and/or sent to Dr. Milan Radovich's lab for future research studies located at:

Walther Hall, Room R3 C240
980 W. Walnut Street
Indianapolis, IN 46202.

In addition, DNA extracted from 9mL of peripheral whole blood will be collected (in a BD Vacutainer EDTA tube) prior to the first dose of therapy for all patients. Extractions will be performed in using a Qiagen DNA/RNA All Prep Kit (Qiagen, Valencia CA). For DNA sequencing, we will employ high-coverage whole-exome chemistry to ensure capture of both structural and nucleotide-level mutations. Briefly, the whole exome sequencing will be performed on our group's own Ion Proton Sequencers. The Ion Proton has been previously demonstrated to produce high-quality exomes for germline variation detection. 100ng of genomic DNA for both tumor and blood normal will undergo library preparation for the Ion Proton Sequencer using the Ion Ampliseq Exome Kit (Life Technologies). This amplification-based method of exome enrichment covers 97% of all consensus coding sequence with >90% of on-target bases covered and >90% coverage uniformity. Sequencing for this project will

utilize the Ion Proton PII chip yielding an estimated 400 million high quality 100bp reads per 4 hour run. In addition, we will also utilize the Ion Hi-Q sequencing chemistry, which uses a new polymerase that results in a 90% reduction in the indel error rate for increased accuracy. All samples will be sequenced to an average of 100X coverage. Each sequencing run will be evaluated for technical quality control metrics including: efficient ion sphere loading, percentage of polyclonality, and mean raw accuracy. Following technical quality control, raw sequencing reads will be mapped to the human genome (hg19) using the highly efficient TMAP algorithm with output in standard BAM format. High confidence SNPs and indel variants will be called using the Ampliseq variant caller which incorporates local re-alignment as well as filtering for homopolymer induced false-positive indels. A minimum of 10 sequencing reads will be needed for a SNP or indel to be called, and only bases with quality values ≥ 20 will be considered. Final variant calls will be reported in standard VCF format. For additional quality review, we will estimate the average transition/transversion (Ti/Tv) ratio per sample. For RNA-sequencing of tumor RNA, libraries will be prepared using the Ion Total RNA-Seq Kit v2 (Life Technologies), followed by emulsion PCR, templating, and sequencing as described above. After quality filtration, we estimate generation of 400 million 100bp fragment sequencing reads per sample. For bioinformatics analysis, reads will be mapped to the human genome using the STAR algorithm; differential expression using Cufflinks, and visualization using Partek Genomics Suite (Partek, Inc). For calling expressed gene fusions, we will use the Tophat-Fusion (Broad Institute) and FusionMap (Amgen) algorithms. Of importance, all genomic data will be stored on the HIPAA-compliant IU Scholarly Data Archive, and all analyses will be performed on secure HIPAA-compliant servers.

4.6.7 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 as per the visit schedule.

4.6.8 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.

4.6.9 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).

Questionnaires on day 15 of cycles 1 and 2, as well as any other questionnaires required at times other than the scheduled visits can be completed by the patient at home and faxed to the Investigator or the authorized study member for evaluation.

• 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.

4.6.10 ECG/ECHO

A standard 12 lead ECG is to be performed at screening, C1D15 and as clinically indicated.

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.

4.6.11 Performance Status

Performance status will be assessed at screening and per the visit schedule. The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale will be used for this study. See Appendix A for details.

4.6.12 Drug Levels and Pharmacokinetic Assessments

- None will be made.

5 Data Management

5.0 Data Collection

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore® at https://cancer.iu.edu/oncore. The OnCore® database is a comprehensive database used by the Clinical Trials Research Office (CRO) and supported by the Indiana University Cancer Center. OnCore® properly used is compliant with Title 21 CFR Part 11.

Access to data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the CRO at 317-274-0930.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Cancer Center Clinical Trials Monitoring Committee.

6 Patient Consent and Peer Judgment

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Research Office) and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

7 Statistical Methods

7.0 General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below.

7.1 Study Design

This is a single arm, open label, two-stage, phase II clinical trial. No randomization or blinding is involved.

7.2 Analysis Population

7.2.1 Enrolled Population

The enrolled population comprises all patients who meet the eligibility criteria and are registered onto the study.

7.2.2 Safety Population

The safety population comprises all patients who have received at least one dose of the study medication. This set will be used for safety analysis.

7.2.3 Efficacy Population

The efficacy population comprises all patients with disease that is radiographically evaluable at initial and at least one follow-up time point. This population will be used for efficacy analysis.

7.3 Sample Size, Accrual and Study Duration

The primary end point of the study is objective response rate (CR+PR) according to RECIST 1.1 criteria for BKM120 monotherapy in patients with advanced thymomas. All sample size estimates are based on the objective response rate.

A two-stage Minimax design will be used with two-sided alpha = .10 and power of 90%. The study will try to rule out a 10% objective response rate (p_0= 0.10) and target a modest response rate of 30% (p_1= 0.30). The study will initially enroll 16 evaluable patients with thymoma; if 0 to 1 of the 16 patients demonstrate a partial response then no further patients will be accrued. If 2 or more of the first 16 patients have a response, then accrual would continue until a total of 25 evaluable patients have been treated. A temporary pause in the accrual to the trial may be necessary to ensure that enrollment to the second stage is warranted. If there are 2 to 4 patients with a response in the total of 25 evaluable patients, then this would be an uninterestingly low rate, while if there were 5 or more patients of the 25 who have a response, this would be sufficiently interesting to warrant further study of this agent in later trials. Under the null hypothesis (10% response rate), the probability of early termination in this cohort is 52%.

It is anticipated that approximately 2 patients per month overall may enroll on this trial. Thus, accrual should be completed in approximately 12-18 months. In order to allow for a small number of in-evaluable patients, the accrual ceiling will be set at 27.

7.4 Patient Characteristics

Baseline patient characteristics will be tabulated, such as demographics (age, race, gender), and ECOG performance score.

7.5 Significant Protocol Violations

Significant protocol violations such as with respect to eligibility criteria and treatment plan will be tabulated.

7.6 Concomitant Medications

Drugs that might affect the study medication, as described in Section 4.0.2, will be tabulated.

7.7 Exposure and Compliance

Exposure to the study medication will be summarized by frequencies and rates of the doses given. Reasons of not completing all doses will be tabulated.

7.8 Efficacy Analysis

The main analysis of the primary endpoint, objective response rate (ORR) after two months, will be based on the safety population (see section 7.12.2 below). The primary efficacy endpoint, ORR (defined as the proportion of patients with the best overall response of PR or CR), together with corresponding 95% exact binomial confidence interval, will be calculated.

A similar analysis will be done for the secondary objective of disease control rate (DCR), defined as the proportion of patients with the best overall response of PR or CR or SD of at least 4 months).

Progression free and overall survival will be determined using Kaplan-Meier curves. Medians and other quartiles for each endpoint will be estimated in addition to the corresponding two-sided 95% confidence intervals. The results of this analysis may be compared in an informal manner to any similarly defined curves available from other published studies in comparable patients with the same disease. We will also repeat all analysis using the efficacy population as supportive analyses.

7.9 Safety Analysis

Toxicities according to CTCAE 4.0 will be summarized by frequencies and rates calculated as the proportion of patients in the safety population experiencing SAEs, discontinuations due to AEs, and AEs. Two sets of tables will be generated: one for the overall toxicities and one for toxicities related to the study medication (possibly related, probably related and definitely related). Toxicities will be grouped by system using MedRA preferred terminology. Grade 1 to 4 will be reported individually and also as grade 3/4. Deaths will be reported individually. AE related to neuropsychological events (depression and anxiety) will also be tabulated.

7.10 Statistical Analysis of Genetic Data

Statistical analysis will include identification of differentially expressed genes, and pathways between tumors than exhibited greater response (CR+PR+SD) compared to those that did not (PD) using two-sample t-tests; association of expressed genes and signatures with response and survival outcome (multivariable logistic and cox regression, respectively); identification of significantly mutated genes associated with response and survival outcome (MutSigCV, which determines significance by testing whether the observed mutations in a gene significantly exceed the expected counts based on a background model); and association of mutational context spectra with response and survival outcomes (Non-Matrix Factorization). In addition, data will also be integrated using a variety of tools designed for multi-platform approaches. This includes network & pathway analyses (IPA and GeneGo); CNV and mutation integrated clusters (IntClust); mutually exclusive modules in cancer (MEMo); drug association databases (Metacore, IPA); and multi-platform cluster of clusters (C-of-C).

7.11 Interim Analysis

Efficacy interim analyses will be performed at described above based on the standard two-stage design.

7.12 Reporting and Exclusions

7.12.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with BKM120.

7.12.2 Evaluation of Response

All patients included in the study who received any study drug must be assessed for response to treatment, even if there are major protocol treatment deviations or if they become ineligible after enrollment. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database].

All of the patients who meet the eligibility criteria and are enrolled (with the exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 are protocol specific and included in section 4.2.2.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

8 Data and Safety Monitoring Plan (DSMP)

Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** are required and will include the principle investigator, clinical research specialist and/or research nurse (other members per principle investigator's discretion). **Monthly** meeting summaries should include review of data and patient safety by including for each dose level: the number of patients, significant toxicities as described in the protocol, dose adjustments and responses observed. Summaries are to be submitted to DSMC@iupui.edu weekly and reviewed monthly.

Study Auditing and Monitoring
All trials conducted at the IUSCC are subject to auditing and/or monitoring. Reports will be reviewed by the full DSMC at the time of study review (Reference Risk Table in full DSMC Charter).

Early Study Closure
At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

Reporting Death
Death will be reported per local IRB reporting guidelines (Section 5.8 of the Unanticipated Problems and Noncompliance SOP).

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PAC coordinator reviews accrual quarterly.

Protocol Deviations
Protocol deviations are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

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APPENDICES

Appendix A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.