BKM120; Investigator Initiated Protocol

A biomarker driven pilot study of the pan-class I PI3K inhibitor NVP-BKM120 in combination with cetuximab in patients with recurrent/metastatic Head and Neck Cancer

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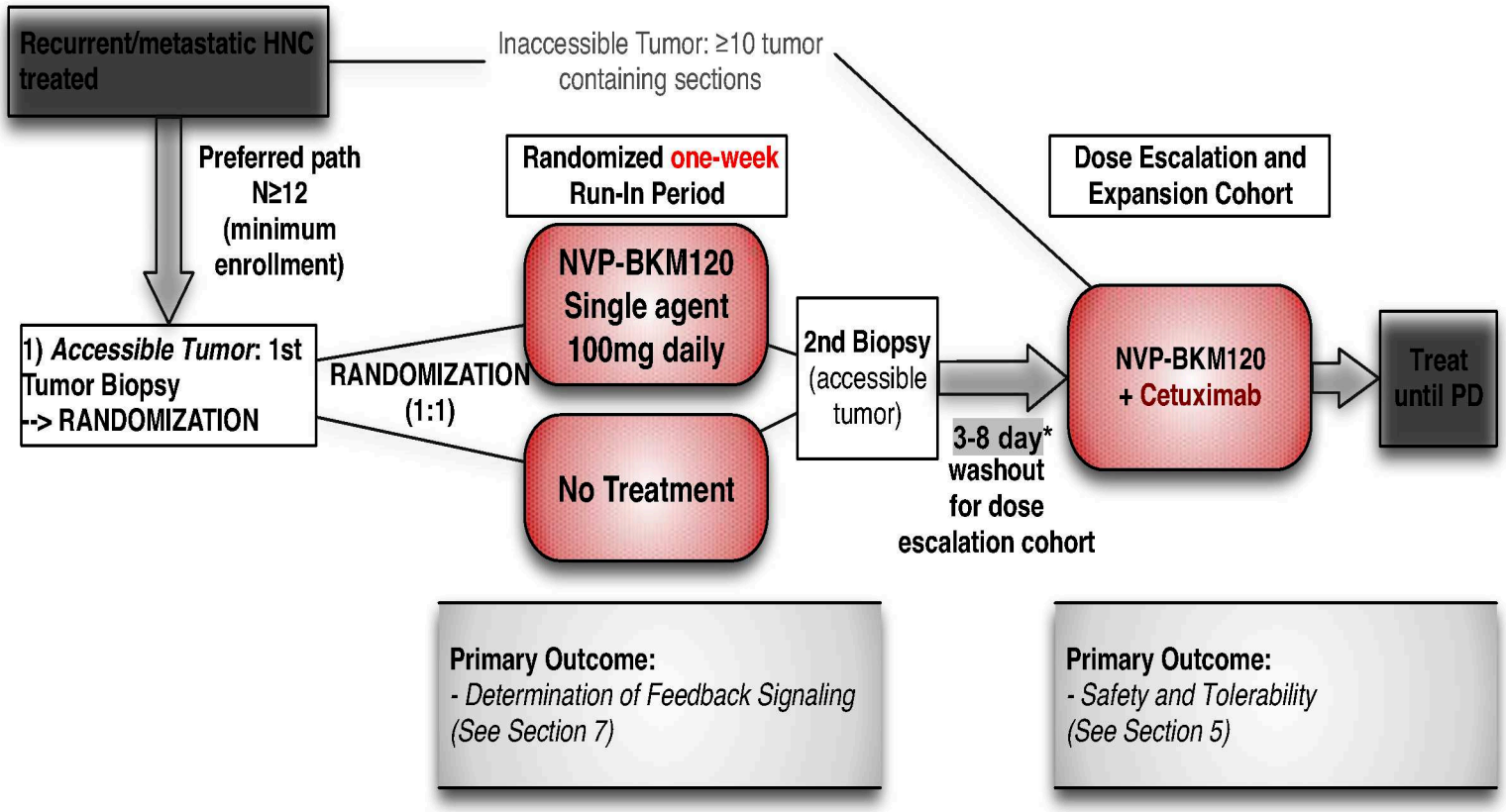
Trial Schema



- A total of 30 patients will be enrolled

*** Washout period only applies to patients who received BKM120 during the dose escalation phase and would start the cetuximab/BKM120 combination phase with a BKM120 dose lower than 100mg daily: Patients, who do not receive run-in period treatment and patients that will receive 100mg of BKM120 + cetuximab per the dose escalation schema can proceed without washout perior and immediately start combination treatment.**

Study Treatment

1. BKM120 – 80mg/100mg (see section 5.2.1 and 5.2.2 and Table 4/page 31), by mouth daily starting Day -7; BKM120 cannot be crushed, and cannot be given via G-tube unless a new formulation becomes available that has been approved by Novartis for such administration.

2. Cetuximab 500mg/m2, iv CI, every 14 days, starting after biopsy (day 1)

→ Please see Treatment/Visit Schedule in Section 4.3.1 (page 61) for additional details.

List of Abbreviations

AE	Adverse Event
AKT	See PKB (protein Kinase B)
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatine Kinase
CK-MB	Creatine Kinase - Muscle and Brain isoenzyme
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
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
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
HDL	High density lipoprotein

IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection fraction
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
NSCLC	Non-small Cell Lung Cancer
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
SCCHN	Squamous Cell Carcinoma of the Head and Neck
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

1.1 Disease Background

Head and Neck squamous cell carcinoma (HNSCC) is the 6th most common cause of cancer death worldwide with more than 600,000 cases annual. In the United States, approximately 40,500 new HNSCC cases and 11,000 deaths were expected in 2006. HNSCC results in significant morbidity because major vital functions such as nutrition, respiration and communication are impaired.

Approximately two thirds of patients with HNSCC will present with locoregional disease and despite aggressive local therapy, close to than half will succumb to recurrent and/or metastatic disease. If untreated, the median survival of patients with metastatic disease is dismal and on the order of 4 months (Bentzen 2005; Ang, Berkey et al. 2002).

In patients with recurrent or metastatic HNSCC, the only therapeutic options are usually palliative consisting of systemic chemotherapy and the EGFR inhibitor cetuximab (Vermorken et al. 2007; Vermorken et al. 2008). Median survival is estimated at 10.1 months using a combination of cisplatin/5-FU/cetuximab. Cytotoxic chemotherapy can have significant toxicities, consisting of bone marrow suppression, nausea/vomiting, rash, hand-foot syndrome, and many others. Better therapeutic options are necessary.

1.2 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.

1.3 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 (Engelman 2009). 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

(Engelman 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 (Engelman 2009). Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers.

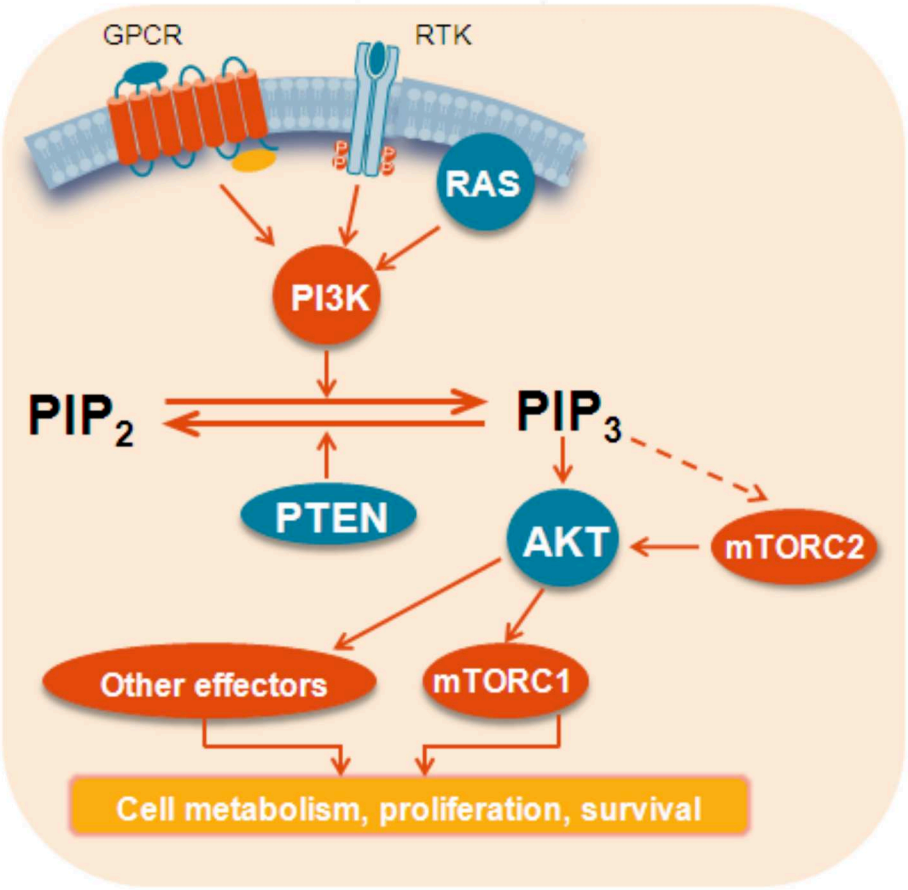
Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to,

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, and others)

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



1.3.1 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 using a luciferase luminescence (class I or III PI3Ks and PI4Kβ) or a TR-FRET assay (Class IV mTOR). The IC50 in these assays is outlined below in Table 1-1:

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

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.

1.3.1.1 Preclinical Safety

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

1.3.1.2 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-p110 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.

1.3.1.2.1 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 rat (< 2 fold).

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

1.3.1.2.2 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.

1.3.1.2.3 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.

1.3.2 Clinical experience

1.3.2.1 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.

1.3.2.1.1 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 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 1-1 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 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 100mg in this study was limited.

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%)
Study Number (n= number of patients treated with 100 mg/d BKM120)	**All grades n (%)**	**Grade 3/4 n (%)**
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.

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, 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 carinii 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 4-6 for more detailed guideline 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 pharmacodynamics 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 (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 4-1.

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, 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.

1.3.2.1.2 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).

1.3.2.1.3 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 04July2011, 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 of 4th July 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.

1.4 Study Rationale

Head and neck cancer (HNC) is the 6th most common cancer worldwide (~50,000 cases/year in the US; 60,000 cases/year in Europe). Once recurrent or metastatic head and neck cancer carries a poor prognosis with a median survival of only 6-10 months (Vermorken et al. 2008; Seiwert et al. 2008).

EGFR is expressed at very high levels in >90% of Head and Neck Cancers (HNC; >NSCLC) and treatment with cetuximab (alone or in combination with chemotherapy or radiation) is now considered a standard of care. Nevertheless the response rate to EGFR inhibitors single agent (cetuximab response rate = 13%, 40-50% stable disease) and median progression free survival of 70 days (Vermorken et al. 2007) remain disappointing. While treatment benefit is generally considered to be comparable to cytotoxic therapies with lower toxicity, the potential of EGFR as a therapeutic target in this highly EGFR expressing disease has not been fully exploited. Clinically treatment for recurrent/metastatic disease is either given in combination with chemotherapy (EXTREME) or after initial cytotoxic chemotherapy.

Cetuximab is the only approved targeted therapy for this disease and the response rate is 13% (Vermorken et al. 2007, Seiwert et al 2012). Better treatments are needed. Based on the published preclinical literature (Ekshyyan et al. 2010) as well as preclinical work done at the Univ. of Chicago we propose to assess the pan-class I PI3K inhibitor BKM120 in patients with head and neck cancer with a focus on PI3K relevant biomarkers that hold potential to identify patients who will benefit from therapy with BKM120 and could be further investigated in an expanded follow-up cohort using biomarker prescreening. The PI3K-AKT-mTOR signaling pathway is active in more than 80% of head and neck cancers (Ekshyyan et al. 2010). Head and Neck cancers have a variety of genetic changes that activate the pathway including EGFR amplification (~30%), PI3K mutations (~10%), and PTEN inactivation (5-10%), as well as other mechanisms which appear to lead to near activation of PI3K signaling in HPV(+) head and neck cancers (Shen/Seiwert EORTC-NCI-AACR meeting 2010, Berlin).

Recently HRAS mutations have been described in 3-5% of HNC (Stransky et al. 2011; Agrawal et al. 2011). Preliminarily such tumors rely heavily on PI3K signaling as well (Rampias et al. ASCO 2011), although further evaluation is indicated.

Preclinical data with PI3K inhibitors (e.g. NVP-BEZ235) suggests strong and widespread synergy (in a panel of 40 cell lines) including in tumors with EGFR amplification. Interestingly EGFR amplification has been found to be a poor predictor of sensitivity to EGFR inhibitor treatment alone and persistent activation of PI3K-AKT signaling is a potential mechanism of resistance (Cohen et al. 2012 (under review)).

It is well established that mTOR and AKT inhibition in several cancer types up-regulates compensatory signaling via irs1 and several other upstream receptor tyrosine kinases (Chandarlapaty et al. 2011). Work by Rosie Xing (in preparation) indicates that the primary mechanism of compensatory RTK up-regulation in head and neck cancers is via EGFR and there is prominent synergy between EGFR and PI3K with co-targeting approaches.

2 Study objectives

Primary

- *One week Run-In (randomized):*

  Induction of **compensatory signaling/feedback loop signaling** after one week of BKM120 (run-in) compared to patients not treated with BKM120 (See Section 7 (Statistical considerations) for details on measurement and power calculation)

- *Combination treatment:*

  Safety and tolerability of combined treatment with BKM120 and cetuximab

Secondary

- Induction of **Apoptosis** after one week of BKM120 (run-in) compared to patients not treated with BKM (See Section 7)
- Tumor Shrinkage (based RECIST V1.1 measurements) in patients treated with combination of

  → Subgroup analysis in patients that are EGFR resistant*
- Response Rate (based RECIST V1.1 measurements) in patients treated with combination of

  → Subgroup analysis in patients that are EGFR resistant*
- Overall Survival
- Progression Free survival

** EGFR resistance is defined as progressive disease (RECIST V1.1) on prior systemic therapy in the recurrent/metastatic disease setting that at a minimum included an EGFR inhibitor and lasted at least 2 weeks.*

3 Exploratory Investigational plan

3.1 Overall study design

Open-label pilot study with serial biopsies in patients with accessible tumor: one pre- and one on-treatment biopsies

→ Please see Schema on page 4

3.2 Study population

3.2.1 Patient population

Patients with recurrent/metastatic head and neck squamous cell carcinoma (HNC) not amenable to curative intent therapy (palliative treatment intent).

Enrollment target: N=30 patients. We estimate to have at least 5 patients with serial tumor biopsies (mandatory for patients with accessible tumor). All patients will have to have tumor material available for biomarker evaluation (for accessible tumors that are deemed save to biopsy fresh biopsies are mandatory; inaccessible tumor - archival tissue is sufficient).

3.2.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, 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:

Inclusion criteria

1. Histologically / cytologically confirmed diagnosis of squamous cell carcinoma of Head and Neck origin not amenable to curative intent therapy. Both HPV(+) and HPV(-) tumors are eligible. Tumors (squamous histology) of unknown primary that are clearly of squamous histology and likely related to the Head and Neck area are eligible.

2. Presence of measurable lesions (RECIST V1.1).

3. Mandatory Tumor biopsy/biopsies in **accessible tumors**. The determination of "accessibility" for biopsy is to be done by the ENT surgeon on examination and/or review of trans-sectional imaging (see Section 4.4 and 4.4.3 for details): mandatory tumor biopsies (1st and 2nd biopsy are mandatory if accessible, 3rd biopsy is optional; see schedule under Section 4.3.1)

   For **inaccessible tumors** (as defined above and in Sections 4.4 and 4.4.3) availability of tissue is required: ≥10 tumor containing FFPE slides/sections; 12-18 ideal)

4. Documented progressive disease/tumor growth, which may include after exposure to a platinating agent (e.g. cisplatin or carboplatin) or another cytotoxic chemotherapy or radiation in a prior line of therapy, or documented intolerance to such an agent. Prior line of therapy may include induction chemotherapy or chemoradiotherapy, in addition to treatment for recurrent/metastatic disease. De novo metastatic disease is also allowed as long as progressive disease/evidence of tumor growth is documented.
5. Age ≥ 18 years
6. ECOG performance status ≤ 2
7. No more than two lines of prior cytotoxic chemotherapy in the recurrent/metastatic (palliative intent) treatment setting
8. Prior use of cetuximab or another EGFR inhibitor is allowable and if used as a single agent should not be considered as a cytotoxic chemotherapy (nor should other targeted therapies be considered as a prior line of cytotoxic chemotherapy).
9. Patients must have at least one site of measurable disease [if applicable] (per RECIST for solid tumors or the appropriate disease classification/criteria for the target population)
10. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb >9 g/dL
11. Total calcium (corrected for serum albumin) within normal limits

12. Magnesium ≥ the lower limit of normal for the institution
13. Potassium within normal limits for the institution
14. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within 1.5 x normal range (or ≤ 3.0 x upper limit of normal (ULN) if liver metastases are present)
15. Serum bilirubin within normal range (or ≤ 1.8 x ULN, e.g. 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), if not consider initiation of metformin treatment prior to study treatment
20. Negative serum pregnancy test within 72 hours before starting study treatment in women with childbearing potential
21. Signed informed consent
22. INR ≤ 2.5

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. No available tumor material for correlative studies (see inclusion criterion 3.)
3. Patients with a known hypersensitivity to BKM120 or to its excipients, or hypersensitivity to cetuximab
4. Inability to swallow BKM120 capsules. (In the future a different formulation of BKM120 may become available and may be approved by Novartis for other routes of administration, which would then supersede this exclusion criteria)
5. More than two prior lines of cytotoxic chemotherapy in the recurrent/metastatic disease setting (palliative treatment intent)(excluding single agent use of an EGFR inhibitor)
6. Patients with untreated brain metastases are excluded. However, patients with treated brain metastases are eligible if they are > 4 weeks from therapy completion (incl. radiation and/or surgery), are clinically stable at the time of study entry and are not receiving corticosteroid therapy at the time of study entry.
7. Patients with acute or chronic liver, renal disease or pancreatitis

8. Patients with the following mood disorders as judged by the Investigator or a psychiatrist, or as a result of patient's mood assessment questionnaire (treating physician to decide on whether to administer 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**. 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 v4 grade 3 anxiety
    - Meets the cut-off score of ≥ 10 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or selects a positive response of "1, 2, or 3" to question number 9 regarding potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)

9. Patients with diarrhea ≥ CTCAE v4 grade 2
10. Patient has active cardiac disease including any of the following:
    - History of clinically significant heart failure (previously assessed) with a left ventricular ejection fraction (LVEF) of < 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
11. 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
12. Patient has poorly controlled diabetes mellitus or steroid-induced diabetes mellitus (HbA1C>7.5%)

13. Patients with **any history of hyperglycemia** (elevated blood glucose level on blood chemistries) should be **considered for initiation of Metformin** treatment (500mg, po, twice daily) prior to starting BKM120. Please also see Tables 4-1 and 4-11.
14. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
    - Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude pneumonitis or pulmonary infiltrates.
15. 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
16. Patients who have been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) $\leq$ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued
17. 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 3-2 or a list of prohibited QT prolonging drugs with risk of Torsades de Pointes.
18. Patients receiving chronic treatment with steroids or another immunosuppressive agent other than specified in Exclusion Criterion #4.
    - **Note:** Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intr-articular) are allowed. Patients with previously treated brain metastases, who are on stable low dose corticosteriods treatment (e,g dexamethasone 2 mg/day, predisolone 10 mg/day) for at least 14 days before start of study treatment are eligible.
19. 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.
20. 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 3-5 for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).

21. 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
22. Patients who have received any continuous or intermittent small molecule therapeutics ≤ 2 weeks (or ≤3 weeks for a monoclonal antibody) prior to starting study drug or who have not recovered from side effects of such therapy.
23. 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
24. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
25. Patients who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant.
26. 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 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 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.

27. Known diagnosis of human immunodeficiency virus (HIV) infection unless patient is fully immunocompetent (CD4>200) and patient is not taking antiretroviral therapy.
28. History of another malignancy within 3 years, except cured basal cell carcinoma of the skin or excised carcinoma in situ of the cervix, or any tumor that is after clearing with the PI clearly not considered to have impact on prognosis.
29. Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

4 Treatments

4.1 Interruption or discontinuation of treatment / Dose Reductions

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 4-1. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0.

(CTCAEv4.0,http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf).

Table 4-0 BKM120 and Cetuximab dose level modification/dose reduction guidelines*

BKM120 Dose Level	BKM120 Dose and Schedule
-1	**60 mg daily**
0*	**80 mg daily***
1	**100 mg daily**
Cetuximab Dose Level	Cetuximab Dose and Schedule
-2	**250 mg/m^2 every 2 weeks**
-1	**400 mg/m^2 every 2 weeks**
0*	**500 mg/m^2 every 2 weeks**

* Starting Dose, ** No BKM120 doses lower than 60mg will be used

*Please note that during the run-in period all patients will take single agent BKM120 100mg po daily. The above dose-escalation table only applies to the cetuximab-BKM120 combination therapy.

Table 4-1

Criteria for interruption and re-initiation of BKM120 and cetuximab treatment

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
No toxicity	Maintain dose level	Maintain dose level
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	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	Maintain dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ 1 dose level	Omit dose until resolved, reinitiate a same dose level
Thrombocytopenia		
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level	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	Maintain dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level	Omit dose until resolved, reinitiate a same dose level

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
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**	**Maintain dose level**
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**	**Maintain 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 study treatment**	**Omit dose until resolved to ≤ Grade 1, then reinitiate at same dose level**
Grade 4 (> 10.0 x ULN)	**Omit dose and discontinue patient from study treatment**	**Omit dose until resolved, and discontinue from study treatment**
AST or ALT		
Grade 1 (> ULN - 3.0 x ULN)	**Maintain dose level with LFTs* monitored as per protocol**	**Maintain dose level**
Grade 2 (> 3.0 - 5.0 x ULN) without bilirubin elevation to > 2.0 x ULN	**Omit dose until resolved to ≤ grade 1, then** • **If resolved in ≤ 7 days, then maintain dose level** • **If resolved in > 7 days, then ↓ 1 dose level**	**Maintain dose level**
Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	**Omit dose until resolved to ≤ Grade 1 then:** • **If resolved in ≤ 7 days, then maintain dose level** • **If resolved in > 7 days, then ↓ 1 dose level**	**Omit dose until resolved to ≤ Grade 1, then reinitiate at same dose level**
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	**Omit dose until resolved to ≤ Grade 1 , then ↓ 1 dose level**	**Omit dose until resolved to ≤ Grade 1, then reinitiate at same dose level**
AST or ALT and concurrent Bilirubin		

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	**Discontinue study treatment permanently.**	**Discontinue study treatment permanently.**
* LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. **Monitoring** (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT.		
ENDOCRINE/METABOLIC		
Fasting Plasma Glucose (FPG)		
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	**Maintain dose level, check FPG every week** • **initiate or intensify medication with appropriate anti-diabetic treatment. In patients not on Metformin, initiate Metformin treatment (e.g. 500mg po twice daily). Generally management is as per investigator's discretion, with Metformin being the first line anti-diabetic agent.** • **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** • **check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks**	**Maintain dose level**

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**
		Maintain dose level

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
	second oral agent if no 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/placebo 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/placebo and ↓ 1 dose level** • **If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from 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**	**Maintain dose level**

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
	(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/placebo 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/placebo** • **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**	**Omit dose, and if BKM120 is discontinued also discontinue Cetuximab, otherwise reinitiate at the same dose**

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
	thirst, polyuria), or presence of blood or urine ketones, discontinue BKM120 and following guidance for management of Grade 4 fasting plasma glucose (FPG).	

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
CARDIAC		
Cardiac – Left Ventricular systolic dysfunction		
Asymptomatic, resting ejection fraction 50 – 40%; or 10-20% drop from baseline	**Maintain dose level**	**Maintain dose level**
Symptomatic, responsive to intervention, ejection fraction 39 – 20% or > 20% drop from baseline	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level** **LVEF measurement to be repeated, if not resolved to ≤ Grade 1 within 3 weeks, permanently discontinue patient from BKM120**	**Maintain dose level**
Refractory or poorly controlled, ejection fraction < 20%	**Omit dose and discontinue patient from BKM120**	**Omit dose and discontinue patient from cetuximab**
Cardiac – QTc prolongation		
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** • **If QTcF remains > 500 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms.** • **Once QTcF prolongation has resolved, BKM120 may be restarted at a one lower dose level** Second Occurrence: • **discontinue patient from BKM120**	**Maintain dose level**
Other Cardiac Events		
Grade 1 or 2	**Maintain dose level**	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**	**Maintain dose level**
Grade 4	**Omit dose and discontinue patient from BKM120**	**Omit dose and discontinue patient from cetuximab**

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
OTHER		
Mood alteration		
*** See Table 4-3 for toxicity grading of mood questionnaires. Questionnaire scores should be considered when assigning the AE Grade but psychiatric consult, if required, may determine the grade**		
Grade 1 (or Grade 2 anxiety if present at baseline)	**Maintain dose level** **Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score**	**Maintain dose level**
Grade 2 (for Anxiety only, if worsened from baseline)	**Institute appropriate co-medication under the guidance of the psychiatrist. Maintain dose level.** • **If the condition does not resolve to ≤ Grade 1 within 14 days despite medical treatment; then ↓ 1 dose level (continue to co-medicate)** **Note**: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level (co-medicate)** Note**: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score**	**Maintain dose level**
Grade 4	**Omit dose and discontinue patient from study** Note**: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for**	**Omit dose and discontinue patient from study**

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
	psychiatric consult regardless of the total questionnaire score	
Rash		
Grade 1	**Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids, minocycline or a macrolide antibiotic)**	**See table 4-2**
Grade 2	**Maintain dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)**	**See table 4-2**
Grade 3	**Omit dose until resolved to CTCAE Grade ≤ 1, then:** • **If resolved in ≤ 7 days, ↓ 1 dose level** • **If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue patient from BKM120**	**See table 4-2**
Grade 4	**Omit dose and discontinue patient from BKM120**	**Omit dose and discontinue patient from cetuximab**
Fatigue (asthenia)		
Grade 1 or 2	**Maintain dose level**	**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**	**Maintain dose level**
Grade 4	**Omit dose and discontinue patient from BKM120**	**Omit dose and discontinue patient from cetuximab**
Other non-hematological adverse events		
Grade 1 or 2	**Maintain dose level**	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**	**If at least possibly related to cetuximab and not amenable to an established, readily effective treatment**: hold cetuximab until resolution to ≤Grade 2. See Table 4.2**
Grade 4	**Omit dose and discontinue patient from study** Note**: Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic**	**Omit dose and discontinue patient from study**
Pneumonitis	**See Table 4.6**	**See Table 4.6**
Cetuximab Infusion Reaction	**Maintain dose level. If cetuximab is permanently discontinued, BKM120 may be**	**See Table 4-2**

Recommended Dose Modifications		
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications for BKM120**	**Recommended Dose Modifications for Cetuximab**
	continued as a single agent if deemed appropriate	
**** Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**		

Table 4-2 Criteria for Cetuximab dose interruption / re-initiation

Management of Dermatologic Toxicity			
Grade 3 Acneform Rash	**Cetuximab**	**Outcome**	**Cetuximab Dose Modification**
1st occurrence	Delay next infusion 1 to 2 weeks (per treating MD)	Improvement	Continue at 500 mg/m^2
		No Improvement	Discontinue cetuximab
2nd occurrence	Delay next infusion 1 to 2 weeks (per treating MD)	Improvement	Reduce Dose Level -1
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay next infusion 1 to 2 weeks (per treating MD)	Improvement	Reduce to Dose Level -2
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Other Cetuximab related toxicities	
Cetuximab Infusion Reaction	• Grade 1 (transient flushing or rash, drug fever <38oC): decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. • Grade 2 (rash, flushing, urticaria, dyspnea, drug fever ≥38oC): stop the cetuximab infusion, administer appropriate therapy, and then restart the cetuximab infusion with a decrease in the infusion rate of 50% and monitor closely for any worsening. • Grade 1 or 2 Infusion Reaction manifesting only as a delayed drug fever (starting after the cetuximab infusion): maintain the cetuximab dose and infusion rate and consider administering acetaminophen or cyclooxygenase-2 inhibitors (at the dose and schedule of the investigator's discretion) prior to the subsequent cetuximab infusion, if not otherwise contraindicated in the patient. • A grade 3 reaction consists of: symptomatic bronchospasm with or without urticaria, requiring parenteral medication(s); allergy-related edema/angioedema; hypotension. • A grade 4 reaction (anaphylaxis) is a life-threatening event characterized by rapid onset (often within minutes) of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. • Treatment of a Grade 3 or 4 Infusion Reaction: Stop the cetuximab infusion immediately and disconnect infusion

	tubing from the patient. Administer epinephrine, bronchodilators, antihistamines (acceptable in this scenario –also see Section 4.2.2), glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. • Following a grade 3 or 4 infusion reaction, the patient is to receive no further cetuximab treatment. In the event of a grade 1 or 2 infusion reaction, the cetuximab infusion rate should be permanently reduced by 50%. • Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further therapy. Appropriate medical therapies include epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen . Patients should be carefully observed until the complete resolution of all signs and symptoms.
Hypomagnesemia	• The incidence of hypomagnesemia (both overall and severe [NCI CTC grades 3 & 4]) is increased in patients receiving chemotherapy and cetuximab as compared with those receiving chemotherapy alone based on controlled clinical trials. Patients receiving cetuximab therapy should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment. •
Drug Fever	• In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. • If a patient experiences isolated drug fever, for the next dose, pre treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses. • If a patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.
Skin toxicities	• Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended. • If a patient experiences severe acneform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. • Management guidelines for treatment of skin toxicities are well established including antibiotics and topical therapies following routine clinical practice.

4.1.1 Monitoring of BKM120 suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Monitoring should include all medically indicated tests appropriate for the respective toxicity and should include the tests/items listed in Table 4-11 under EOT (end of therapy) at least once. If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study. If the patient requires more than 2 dose reductions, the patient should be discontinued from the study (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 3.4.4.2. No BKM120 dose level below 60mg daily will be assessed (unless the protocol is amended accordingly).

4.1.2 Known Undesirable Side Effects of BKM120

4.1.2.1 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 CTCAE Grade $\geq$ 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.

4.1.2.1.1 Management of mood alteration

In patients with evidence of mood problems (assessed by the treating oncologist/investigator), or a history of mood problems a patient self-rating mood questionnaires PHQ-9 (depression) and GAD-7 (anxiety) will be used:
• to support assessment of eligibility at Screening
• to monitor for newly occurring or worsening mood alterations during the study.
The following grading system will be used for this study:

Table 4-3 Toxicity grading based on mood questionnaire scores

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

At Screening, a patient as judged by the investigator or who meets the cut-off score of ≥ 12 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or select a positive response of '1, 2, or 3' to question number 9 regarding suicidal thoughts or ideation will be excluded from the study.

During the study, patients who meet the cut-off score of ≥ 10 (≥ CTCAE grade 2 mood alteration) in either questionnaire or indicate a positive response by selecting '1, 2, or 3' to question number 9 on the PHQ-9 must see a psychiatrist for advice on the most appropriate medical treatment must see a psychiatrist for diagnosis and determination of most appropriate medical treatment. For anxiety, this applies only if status has worsened from baseline. Patients who experience ≥ grade 2 mood alteration will be followed twice weekly by patient self-rating mood scale and will be seen weekly by the psychiatrist until resolved ≤ grade 1 or baseline (for anxiety). Questionnaire responses will be checked by the psychiatrist at the weekly visits (until resolution to Grade 1 or baseline (for anxiety).

Table 4-4 GAD-7 anxiety scale

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

Column totals: _____ + _____ + _____ + _____

= Total Score _____

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

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

Table 4-5 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 _____

4.1.2.2 Hyperglycemia

In preclinical studies, insulin/glucose homeostasis was impacted in various species (mice, rats, dogs), as expected from the mode of action of BKM120. In both rats and dogs, at the doses used in the 4-week studies, these effects were minimal. However, in mice treated at high doses (30 or 60 mg/kg/day) a clear induction of insulin resistance/insensitivity was observed, 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 4-1 and 4-11. Any patients with a history of hyperglycemia should be considered for initiation of **metformin therapy** prior to starting BKM120.

4.1.2.2.1 Management of severe Hyperglycemia

In addition to the dose modification, metformin treatment, and additional hyperglycemia treatment guidelines in Table 4-1 the following steps should be taken for persistent hyperglycemia:

- 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.

4.1.2.3 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.

4.1.2.3.1 Management of Cardiac events

At the screening visit a 12-lead electrocardiogram (ECG), and assessment for history/symptoms of heart failure will be performed. In patients with a history/clinical symptoms of heart failure a MUGA scan (echocardiogram acceptable) will be performed to assess clinical status and eligibility. Repeat ECGs will be performed at screening and as clinically indicated. A MUGA will be performed/repeated if any symptoms consistent with cardiac problems occur.
In the prior phase I study of BKM120 (Bendell et al. 2012) no evidence of changes in ejection fraction/heart failure symptoms were reported. Cetuximab does not affect cardiac function and prior reports suggest tolerability of the combination of a PI3K inhibitor and cetuximab (Senzer et al 2011 AACR-NCI-EORTC meeting A174).

4.1.2.3.2 Management of Pneumonitis

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

In ongoing clinical trials with BKM120 in the single agent setting two cases of Pneumonitis occurred. In the study BKM120X2101 one patient experienced Pneumonits grade 2 eight weeks after the first dose of BKM120 at 100mg which resolved in 7 days after antibiotic therapy and discontinuation of the study treatment due to fatigue. In the Japanese study BKM120X1101 one case of Pneumonitis occurred in a 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).

All patients participating in clinical trials administering BKM120 will be routinely asked about the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function test should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed Pneumonitis. In case of a documented Pneumonitis, the guidelines (including dose modifications) in Table 4-6 should be followed. Consultation with a pulmonologist is highly recommended for any Pneumonitis case identified during the study.

Table 4-6 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 until return to within normal limits.	No specific therapy is required	Administer 100% of BKM120 dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce BKM120 dose by 1 dose level (see Table 4-0/page 22) until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with BKM120 until recovery to ≤ Grade 1. May restart study treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	BKM120 Dose Adjustment
	BAL is recommended.		
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with BKM120.

*The dose of cetuximab will not be adjusted for pneumonitis. Upon discontinuation of BKM120 cetuximab should also be discontinued.

4.1.2.3.3 Management of Liver Toxicities

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

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

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

4.1.2.4 Study discontinuation

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

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will

be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

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

4.2 Treatments

4.2.1 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. A new formulation may become available in the future and guidelines for administration per Novartis should be followed. 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, on the days of full pharmacokinetic sampling, the exact time of any episodes of vomiting within the first 4 hours post-dosing on that day and within the first 4 hours following the previous day's dosing must be noted whenever possible.

If the patient forgets to take her/his dose before 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.

4.2.2 Cetuximab Administration

- Cetuximab will be given on an outpatient basis every two weeks intravenously at a dose of 500mg/m^2 (given over 120 minutes the first time, the over 60 minutes subsequently) (all iv).
- Patients will receive cetuximab intravenous infusions via infusion pump. The dose of cetuximab is 500 mg/m^2 and is administered over 120 or 60 minutes. The dose of cetuximab is dependent upon the patient's baseline body weight in kilograms (mg/kg). If there is a ≥20% change in body weight from baseline this dose should be recalculated. The infusion rate must not exceed 10 mg/minute (5 mL/minute). Patients should be observed closely during cetuximab infusion and for **60 minutes after the infusion**. Infusion times may be increased for patients who experience mild allergic reactions, but cannot exceed 4 hours. Prior to infusion, the appropriate volume of cetuximab will be drawn from the vial with a sterile syringe and cetuximab will be transferred from the syringe into a sterile evacuated container. Cetuximab will be filtered through a 0.22-µm protein-sparing or low- protein binding in-line filter. After infusion, 0.9% normal saline will be used to flush the line.
- Premedication with an H_1 antagonist (diphenhydramine 25-50 mg I.V. or oral) 30 minutes prior to infusion should be given for allergic reaction prophylaxis. 50mg should be administered prior to the first dose of cetuximab in an effort to prevent an infusion reaction.
- Four weeks (28 days) constitutes one cycle of treatment.
- If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, please refer to Table 4-2. Infusion reactions to cetuximab may be severe and can occur during or after treatment. Use of H2 blockers is not recommended due to interactions with BKM120. At the physician's discretion, H2 blockers may be used, but should be administered more than 60minutes after BKM120 (H2 blockers other than cimetidine should be considered due to additional drug interactions of cimetidine). Cetuximab administration may be resumed at the physician's discretion. Re-attempting infusion at a slower rate, possibly over one hour is appropriate. Additional treatment of severe allergic reactions is at the discretion of the treating physician and may include corticosteroids as well as other agents.
- As a routine precaution, patients enrolled in this study will be observed closely for any potential adverse events by the medical staff for the duration of the cetuximab infusion and until at least 1 hour after the end of the initial infusion, in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the

immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. Patients should be instructed to report any delayed reactions to the investigator immediately.

- Details about dose reductions / resumption of therapy on subsequent treatment days are provided in Section 4 / Tables 4-1 and 4-2.

4.2.3 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 below (Sections 4.2.3.1, and 4.2.3.2).

4.2.3.1 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 4-7 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 4-7 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 4-8 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, 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 4-7 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

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche et al. 2008).			

All QT-prolonging drugs listed in Table 4-8 are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 4-10 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.

Table 4-8 List of prohibited QT prolonging drugs

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	
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

Drug	QT risk(*)	Comment
		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.

4.2.3.2 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 4-9 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 hyperglycemia/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 4-8 for a list of QT prolonging medications to be used with caution.

Note: please refer also to Table 4-8 for a list of **prohibited** QT prolonging medication.

- Please refer to Table 4-9 for 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 corticosteriods is allowed (e.g. for chronic obstructive pulmonary disease, or as an anti-emetic). Chronic dosing of corticosteriods is known to induce CYP3A enzymes, thereby increasing the risk or reducing BKM120 overall exposure to sub-therapeutic levels.

Table 4-9 List of CYP450 Substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	Adinazolam	felodipine1
cerivastatin	diclofenac	citalopram	alfentanil1,2	fentanyl2
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine1	flunitrazepam

repaglinide	fluvastatin	clomipramine	Alprazolam	fluticasone1
rosiglitazone	glibenclamide (glyburide)	clopidogrel	Amlodipine	lovastatin1
torasemide	gliclazide	diazepam	Aripiprazole	maraviroc1
troglitazone	glimepiride	fluoxetine	Atorvastatin	midazolam1
	glipizide	imipramine	Brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam1	nisoldipine
	irbesartan	mephobarbital	budesonide1	nitrendipine
	ketobemidone	moclobemide	buspirone1	perospirone1
	lornoxicam	omeprazole	Capravirine	quinine
	losartan	pantoprazole	Cerivastatin	sildenafil1
	meloxicam	progesterone	Chlorpheniramine	simvastatin1
	naproxen	quazepam	cyclosporine2	sirolimus1,2
	nateglinide	rabeprazole	darifenacin1	tolvaptan
	piroxicam	sertraline	Diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine2	triazolam1
	S-ibuprofen		ebastine1	
	sulfamethoxazole		eletriptan1	
	tenoxicam		eplerenone1	
	tolbutamide		ergotamine2	
	torasemide		Estazolam	
	valdecoxib		everolimus1	

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

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

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

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

Table 4-10 List of QT prolonging drugs to be used with caution

Drug	QT risk	Comment

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	

Drug	QT risk	Comment
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	
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	

Drug	QT risk	Comment
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		

4.2.3.3 QTc Calculation and Formula

QTc interval is defined as the QT interval corrected for heart rate. The following formula is to be used:

QTc = QT / (RR)^1/2 (Bazett's Formula)

RR is the interval from the onset of one QRS complex to the onset of next QRS complex

QT is the measure of time between the start of the Q wave and the end of the T wave in the heart's electric cycle.

4.3 Visit schedule and assessments

4.3.1 Visit Schedule

Table 4-11 Evaluation and visit schedule

Examination	Screening/ Baseline	Only for pts. undergoing biopsy: 1 week run-in (Days -7 to -1)[15]	After optional Washout period[16] Cycle 1 (Days 1 to 28)		Cycle 2		Cycle 3 and additional cycles							
Day of Cycle	**-28 → -8**	**-7**	**C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**C4 D1**	**C4 D15**	**C5 D1**	**C5 D15**	**…**	**EOT**
Informed consent	X													
Medical History	X													
BKM120[11]		X……continuous daily dosing……X												
Cetuximab[12]			X	X	X	X	X	X	X	X	X	X	X	
Inclusion/exclusion criteria	X													
Tumor biopsy (accessible tumor only)	X	X[14]											X[10]	
Archival tissue (≥10 unstained slides)[13]	X													
Research blood draw for normal DNA (part of routine draw)	X													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination (including skin rash assessment)	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
Neuro-psychiatric assessment (per the treating MD and/or self rating mood questionnaire)[1]	X	X	XX[17]	X X[17]	X	X	X		X		X		X	X
MUGA	Optional (only when indicated clinically)[2]													
12-lead ECG	X		As clinically indicated.											
Radiological tumor assessment/response assessment (CT Scans)[4]	X						X				X		X[4]	X
Hematology[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[6]	X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X
Add-on Chemistry[7]	X				X				X				X	X
Coagulation Profile[8]	X				X								X	X
Fasting plasma glucose[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test (within 72h of starting drug, can be done on first day of treatment before taking BKM120)	X													X
Metformin Check[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] If felt to be indicated by the treating physician PHQ-9 and GAD-7 questionnaires will be completed at each visit through the end of Cycle 2. Starting with Cycle 3, assessments are to be done on Day 1 of each cycle. Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study.

[2] MUGA indicated ONLY in patients with a history of heart failure/symptoms of heart failure only. Reassessment at Cycle 4 and anytime cardiac symptoms occur should be considered. If indicated an echocardiogram may also be used, but preferred assessment is by MUGA (See section 4.1.2.3.1).

[3] Any elevated blood sugar level should trigger initiation of Metformin (e.g. 500mg po twice daily) or modification of the antidiabetic regimen (as per Table 4-1). Any history of hyperglycemia should trigger consideration of Metformin in order to prevent further hyperglycemia.

[4] Screening radiological assessments should be performed within 4-8 weeks of the first dose and at any time if respiratory symptoms occur. Radiological tumor assessment should be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks, until progression of disease or end of treatment. All assessments should be performed within ±7 days of the scheduled day of assessment. The assessment at the EOT visit is only to be performed if the prior assessment occurred ≥ 28 days before.

Comparable alternative imaging modalities may be used (MRI/PET) if indicated.

[5] 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.

[6]Serum chemistry: K+, Na+, Ca++, Mg++, bicarbonate, creatinine, BUN, ALT, AST, total bilirubin (fractionation only required if total bilirubin is >2, also if bilirubin is >2x NL GGT should be added), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher)

[7]Serum chemistry add-on: total cholesterol (if abnormal add HDL, LDL, triclycerides), amylase (add lipase if amylase abnormal). All draws should occur within 48 hours of the intended visit. To be drawn at baseline, at cycle 2, cycle 3 and then every 4 cycles.

[8] Coagulation - PT or INR, PTT. To be drawn at baseline, at cycle 2, cycle 3 and then every 4 cycles.

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.

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

[10] 3rd Tumor biopsy is optional and should be performed at tumor progression in patients, who previously responded to treatment.

[11] BKM120 is given daily and self administered by the patient

[12] Cetuximab is given every 14 days starting cycle 1. During cycle 3 and thereafter patients continue to receive cetuximab every 2 weeks, but visits with the physician are only every 4 weeks.

[13] Can be substituted with tissue from the fresh biopsy (if sufficient material available)

[14] Tumor on-treatment biopsy (2nd biopsy) should occur after at least 6 days of BKM120 treatment. On the day of biopsy the BKM120 dose should be taken 2h before the scheduled biopsy, and the actual biopsy should occur 2-4h after the BKM120 dose.

[15] For patients who will undergo biopsy (accessible tumor) a 7-day run-in period with either BKM120 (100mg po daily) or no treatment will be done. Patients who do not undergo biopsy (archival tissue only) will skip the run-in period and start directly with Cycle 1 day 1.

[16] For patients who received BKM120 as part of the 7-day run-in period AND are part of the initial dose escalation cohort, there is a 3-8 day washout period (minimum 3 days, maximum 8 days) prior to starting combination treatment. Patients who do not receive BKM120 during the run-in period AND patients that will receive 100mg of BKM120 daily together with cetuximab (after the dose-escalation period) may proceed immediately with combination treatment.

[17] Cycle 1 Day 7, and Cycle Day 22 should include an additional neuropsychiatric assessment, which could either be done in the office, or if inconvenient for the patients (e.g. travel distance) via phone call.

Shaded boxes indicate optional/facultative procedure -> see comments under 15/16 or protocol text.

4.3.2 Efficacy assessments (Response)

For the purposes of this study, patients should be reevaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer EA et al, Eur J Ca, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

4.3.3 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry 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.

Generally cetuximab has been well tolerated in combinations with other targeted and chemotherapeutic agents, and combinations of PI3K inhibitors with HER family blocking agents are now widely being investigated with not reported evidence of severe adverse events to date. Stringent dose reduction measures have been implemented (see Section 4.1, page 22).

Section 5 describes the dose escalation schema and definition of dose limiting toxicities.

Post-Biopsy patients will be followed closely for any evidence of complications. Dose delay/reduction rules will be closely followed as outlined (see Section 4.1, page 22). In addition the PI may elect to further delay treatment if any serious concerns about wound healing or unexpected events should occur.

4.3.4 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.

4.3.4.1 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.

4.3.4.2 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **Serious and expedited AEs reported as described below must <u>also</u> be reported in routine study data submissions.**

4.3.4.3 Serious adverse events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (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.

ALL Serious Adverse Events, whether or not they are considered related to the study agent MUST be reported to the sponsor-investigator and to the University of Chicago Comprehensive Cancer Center (UCCCC). Refer to Section 4.3.6 for reporting guidelines.

4.3.5 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater frequency than expected.

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, investigator brochure, FDA-approved package insert, or elsewhere in

the current IND application. This includes adverse events listed in the protocol, consent or IND as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with this investigational agent.

ALL SUSARS occurring on this clinical trial must be reported to the FDA. Refer to Section 4.3.8 for reporting guidelines. The UChicago CCTO will be responsible for all FDA communications on behalf of the IND Holder. Individual sites should not submit any correspondences directly to the FDA.

4.3.6 Reporting Mechanism / Requirements for the University of Chicago Comprehensive Cancer Center

All serious adverse events (as defined in section 4.3.4.3) and protocol violations/ deviations must be reported to the UCCCC Cancer Clinical Trials Office (CCTO) in accordance with the UCCCC Data Safety Monitoring Plan.

The responsible party reporting the event (the RN/CRA at the University of Chicago or at a participating site) should notify the PI, the Medical Monitor at the University of Chicago and the University of Chicago Comprehensive Cancer Center Clinical Trials Office (CCTO). The RN/CRA should subsequently report the event to Novartis as required by regulation and agreement; this process is described below.

Reporting must be performed within 24 hours of the investigator or staff becoming aware of the event by calling and e-mailing the QA Operations Coordinator at (773) 702-0819 / qaccto@bsd.uchicago.edu as well as e-mailing the details of the event to the PI, the Medical Monitor and to the Regulatory Manager identified on the cover page. When sending in the 24-hour notification, please provide the following:

- Your name, site name, and telephone number
- Subject initials
- Subject study number
- U of C IRB protocol number
- Lead Investigator of study
- Treating physician
- Date of event
- Description of the event (including grade of the event, whether or not the event required hospitalization or resulted in the death of the patient).

All SAE's reports regardless of grade or attribution should be sent to Novartis Pharmaceuticals. See section 4.3.10 below

The SAE report should also be submitted to the institution's IRB according to institutional guidelines (see 4.3.7).

4.3.7 Reporting Requirements for the Institutional Review Board

At the University of Chicago: Events meeting current IRB reporting criteria must be submitted by the principal investigator via the IRB's electronic submission system within **the IRB's designated reporting timeframes**. Details of the IRB's current reporting policy and timelines can be found on their website at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html

The responsible research nurse and/or clinical research associate/data manager are responsible for entering the appropriate information into the IRB's electronic submission system and forwarding the submission to the principal investigator for reporting to the IRB.

At other centers: the respective current IRB reporting criteria should be used – and should be comparable to the requirements listed above for the University of Chicago.

4.3.8 Reporting Requirements for the FDA

This study will be conducted under an IND held by Tanguy Seiwert, MD at the University of Chicago.

Per 21 CFR 312.32, the sponsor-investigator is required to notify the FDA and all participating investigators of potential serious risks within 15 calendar days of determining the information meets FDA reporting requirements.

Unexpected fatal or life-threatening suspected adverse reactions must be reported to the FDA by the sponsor-investigator via phone or fax within 7 calendar days.

Current FDA regulations require that all SUSARs (see definition in section 4.3.5) occurring on this trial, other findings that suggest a significant risk to humans exposed to the investigational drug (e.g. information from pooled analysis of multiple studies), and any clinically significant increase in the rate of an expected serious adverse reaction be reported as an IND Safety Report. Refer to Table A below for guidelines for reporting these events to the FDA.

In order to meet these requirements, the sponsor-investigator will review all reported serious adverse events as they occur and will conduct a literature search to seek new safety information and review and analyze all safety information from this clinical trial at least annually and more frequently as appropriate.

Table A: Reporting Requirements

Report Type	Method of Report	Responsible Party	Timeline[1]	
			Fatal/Life-Threatening Event	
			Yes	No
Individual Report	Form 3500A (MedWatch)[7]	RN/CRA	4 calendar days[5]	10 calendar days[5]
Other Findings that Suggest *Significant Risk*[2]	Narrative[3]	PI	4 calendar day[6]	10 calendar days[6]
Clinically Significant Increased Frequency of Suspected Adverse Reactions[4]	Narrative	PI	4 calendar days[6]	10 calendar days[6]

1: Report Due to CCTO IND Coordinator according to the specified timeline regardless of whether or not all information regarding the event is available. If applicable, a follow-up report should be provided to the IND Coordinator once additional information on the event is available.

2: An IND Protocol Amendment is also required to describe any changes to the protocol, consent, or overall conduct of the study made as a result of this information. All revised documents should be made available to the CCTO IND Coordinator at the time of IRB submission.

3: Copy of relevant publication(s) should be included if applicable.

4: Details of individual cases should be included as appropriate

5: From date event was reported to the sponsor-investigator

6: After information is received by the investigator and determined to meet reporting criteria

7: Copy should be maintained in the subject research chart and master IND file in the CCTO.

All other events (e.g. protocol deviations or other safety concerns) not meeting the requirements for IND Safety Reporting (per 21 CFR 312.32) but which require reporting to the IRB as an Unanticipated Problem will be reported to the FDA as an informational amendment or with the annual report as appropriate.

4.3.9 Data and Safety Monitoring

Data Safety and Monitoring (DSM) will occur at the weekly University of Chicago Head and Neck meetings, which are led by senior level medical oncologists. At each meeting, all active studies are reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form documenting the discussion outcome with respect to patient safety, risk level and study

continuation will be filled out for this protocol and signed by either the principal investigator, or by his designate if not available.

The study will be audited as per the Audit Program described in the UCCCC Data Safety Monitoring Plan. Patient charts will be audited for protocol compliance items including eligibility, completion of procedures, administration of treatment, reporting of toxicities, documentation of response, follow-up, data-collection, record keeping, and the collection of quality of life and correlative studies.

All participating institutions will receive a trial summary every Monday that will be transmitted by e-mail to the principal investigator at the affiliate site. This summary will inform the affiliate institutions of the following:

- Number of patients accrued to the protocol, both
- Number of openings available
- Any change in the status of the protocol including temporarily on-hold and closed to accrual
- DSM meeting minutes

4.3.10 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E). Applicable events will be reported to the IRB and FDA as per their current policies.

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.

4.3.10.1 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) 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.

4.3.10.2 Laboratory evaluations

Pregnancy Test

A serum pregnancy test (β-HCG) is required for all women of child-bearing potential at screening, within 72 hours prior to the first dose of BKM120 (can be done just prior to the first administration of BKM120 (Day -7). 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 if clinically indicated.

Hematology

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

Coagulation Profile

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

Serum chemistry

Biochemistry includes the following parameters: K+, Na+, Ca++, Mg++, ALT, AST, total bilirubin (if abnormal: direct and indirect), creatinine, GGT (only in case of elevated bilirubin), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, glucose, urea or BUN

The add-on chemistries will be performed less frequently and include: total cholesterol (if abnormal add on: HDL, LDL, triglycerides), amylase (if abnormal add lipase),

All draws should occur within 48 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.

4.3.10.3 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 in the sitting position as per the visit schedule.

4.3.10.4 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.

4.3.10.5 Neuropsychiatric assessments

Patient self-rating mood questionnaires for anxiety and depression (PHQ-9, GAD-7) will be applied if deemed indicated by the treating physician and can be initiated at the following time points:

• Screening and Day -7

• Days 1 and 15 of Cycle 1

• Day 1 and 15 of Cycle 2

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

• End of Study treatment

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

4.3.10.6 ECG and MUGA

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

MUGA will only be performed to assess eligibility in patients with a history of heart failure / hear failure symptoms to determine eligibility. MUGA may be repeated anytime clinically indicated e.g. if symptoms of heart failure develop. An echocardiogram (ECHO) may be performed alternatively if a MUGA is contraindicated. See section 4.1.2.3.1 for additional details.

4.3.10.7 Performance status

Performance status will be assessed at screening and per the visit schedule using ECOG scale (Appendix A).

4.4 Correlative Studies and Tissue Collection Tumors

While requirements for tissue and correlational studies are clearly stated and are to be implemented stringently, medical necessity, e.g. in the case of potential harm to the patient, or other extenuating circumstances may trigger a review and possible waiver per the PI on rare occasions.

4.4.1 Assessment of Accessible tumor

Tumors in the upper aerodigestive tract and larger metastatic deposits in other organ systems (e.g. a large peripherally located lung metastasis) without undue risk medical risk are considered accessible for biopsy. Patients with accessible tumors that are deemed safe for biopsy are mandated in order to participate in the protocol to undergo an initial (pretreatment) and second on-BKM treatment biopsy (run-in period). A third biopsy during the combined treatment is optional. The PI and the treating physician will decide whether a tumor lesion is considered accessible prior to initiation of therapy, and this assessment is only to updated if the patients disease status or medical status changes significantly.

4.4.2 Archival Tissue and Blood.

All patients are required to provide ≥10 unstained FFPE slides (18-20 slides is considered ideal). This requirement can be waived ONLY if a fresh tumor biopsy provides adequate tissue.

Furthermore all patients are required to collect blood for banking of normal DNA

→ See Appendix B for tissue collection form

4.4.3 Tumor Biopsies

Based on clinical examination and/or review of cross-sectional imaging and ENT surgeon will make the assessment whether a tumor is 'accessible' or 'in-accessible' for biopsy. Tumors that have been deemed to be accessible for biopsy will be biopsied by an ENT surgeon (excisional biopsy or core needle biopsy) or via interventional radiology (core biopsy). A large (several pass) bronchoscopic biopsy is potentially also acceptable, but a discussion about the amount of required tissue between the PI and the pulmonary attending performing the procedure is required prior to biopsy. Other specialties (e.g. surgeons from other organ areas) may also be involved in obtaining tissue/biopsies.

The first and second biopsy are mandatory in patients with accessible tumor, the third biopsy is to be considered in patients who previously responded and subsequently progressed. The third biopsy may also be obtained in patients without prior biopsy (in setting of prior response and subsequent progression).

4.4.3.1 Timing of biopsies

The timing of biopsies can be handled flexibly as long as the following requirements are fulfilled.

Pre-treatment Biopsy:

- Pretreatment biopsy occurs prior to administration of first dose of BKM120

On-treatment Biopsy / 2nd Biopsy:

- On treatment biopsies (2nd biopsy) should occur at least 6 days after initiation of treatment with BKM120
- The PI can extend the run-in period by up to 10 days if required in order to allow the mandatory 2nd biopsy
- On the day of the biopsy the dose of BKM120 should be administered 2 hours prior to the planned biopsy, and the actual biopsy should occur 2-4 hours after administration of BKM120.

3rd Biopsy:

- The third biopsy should be taken at any time point after progression on BKM120/cetuximab is demonstrated

4.4.3.2 Biopsy safety considerations

Biopsies (Core biopsies and small excisional biopsies) are generally considered safe during administration of treatment (based on prior experience with cetuximab).

Nevertheless in difficult to assess/high risk locations the treatment should be held for 2-5 days prior to resuming therapy. For larger scale surgeries or should bleeding or wound healing complications arise the PI can decide to continue holding therapy and will assess how long to hold treatment on a cases by case basis.

4.4.4 Correlative Studies

The following correlative studies are planned and are mentioned in the consent form for patients. Since correlative studies are not covered under the current clinical trial budget additional internal funding will be sought via the University of Chicago Cancer Center, CTSA grant, or other funding agencies. Such a follow-up proposal will contain the detailed methodology. At a minimum assessment of PIK3CA mutation status (Sanger Sequencing), and PTEN expression (IHC) will performed even in the absence of additional funding.

At baseline (archival tissue, or obtained from a new biopsy):

1. PI3K related mutation testing (PIK3CA, but additional PI3K members/related genes may be tested). Anticipated analysis methods: Sanger sequencing of PIK3CA (or equivalent method; subject to change)
2. PI3K related copy number testing (PIK3CA). Anticipated analysis methods: qPCR of PIK3CA gene (or equivalent method; subject to change)
3. HRAS mutation testing; Anticipated analysis methods: Sanger sequencing of HRAS (or equivalent method; subject to change)
4. Evaluation of PTEN/INPP4B evaluation (other tumor suppressors may also be evaluated); Anticipated analysis methods: Immunohistochemistry (or equivalent method; subject to change)
5. HPV status; Anticipated analysis methods: p16 immunohistochemistry or HPV ISH (or equivalent method; subject to change)
6. Normal and Tumor RNA and DNA and protein for possible additional studies (Patients to specifically consent to banking). Studies could involve more advanced genomic analyses including array based approaches or next generation sequencing.

New biopsies in addition will be assessed for the following:

1. RTK phosphorylation; Anticipated analysis methods: PamGene Kinase Array Platform available in the Seiwert/Salgia Laboratories (or equivalent method; subject to change). We will specifically look for an increase (from baseline/pre-treatment biopsy) in:
    a. **pEGFR**
    b. pHER3
    c. pIRS1

2. Apoptosis/Autophagy evaluation; Anticipated analysis methods: TUNEL staining (e.g. TUNEL apoptosis detection kit (GenScript), or an equivalent method; subject to change)
3. Differential gene expression; Anticipated analysis methods: gene expression arrays (or equivalent method; subject to change)
4. P-4EBP1 staining; Anticipated analysis methods: Immunohistochemistry (or equivalent method; subject to change)

5 STUDY DESIGN

The study will consist of two separate phases: a dose-escalating Phase I study followed by a fixed dose expansion cohort.

5.1 Design of the 1-week Run-In period

Patients will be randomized between BKM120 given at the recommended Phase II dose (Bendell et al 2012) of 100mg daily, or no treatment (non-blinded) and after one week will undergo biopsy (both BKM120 and untreated cohort).

Patients treated with BKM120 will have a one week wash-out period (can be prolonged if side effects require as per the treating physician).
Patients not treated with BKM120 may start combination treatment immediately – either as part of the dose escalation cohort (see 5.2) or the Expansion Cohort (see 5.3).

5.2 Design of the Dose Escalation Cohort

The dose escalation phase will assess the safety and tolerability of BKM120 in combination with cetuximab in up to 12 patients.
With the exception of rash there are no significant overlapping toxicities between cetuximab and BKM120 (Bendell et al 2012), and prior experience with combination of the PI3K inhibitor PX-866 with cetuximab have been well tolerated at full dose of both agents (Senzer et al 2011 AACR-NCI-EORTC meeting A174). Combination of BEZ235 with the HER2 antibody Trastuzumab has also been well tolerated (Krop et al.J Clin Oncol 30, 2012 (suppl; abstr 508))

Based on experience in other BKM120 combination studies and discussion with Novartis we will initiate treatment of BKM120 at 80% of the Phase I defined phase II dose (Bendell et al 2012): 80mg; subsequently we will dose escalate to 100mg (= recommended Phase 2 dose) at the next dose level (see below). BKM120 dose may be reduced down to 60mg as needed, and per the guidance of Novartis no dose level lower than 60mg should be used.

5.2.1 Determination of the Maximum Tolerated Dose (MTD)

Patients will be carefully assessed with regards to safety and tolerability, using NCI Common Terminology Criteria (Cancer Therapy Evaluation Program (CTEP) CTCAE, Version 4.0).

The starting dose of BKM120 will be 80mg daily in combination with full dose of cetuximab given biweekly (500mg/m2)

There will be no intra-patient dose escalation. Dose escalation will proceed according to a standard "3+3" design. That is, three patients will be entered at each dose level and if 0 out of 3 develop a DLT, three patients will be entered at the next higher dose level. If 1 out of 3 experiences a DLT, three more patients will be entered at the same dose level for a total of 6. Then if none of these three has a DLT dose escalation will continue. If $\geq$ 2 of the 3-6 patients treated in a cohort experience a DLT, dose escalation will stop and three additional patients will be entered at the next lowest dose level (see BKM120 dose levels Section 4.1/Table 4-0) if only three patients were treated previously at that dose. Dose escalation is allowed to proceed if all patients have completed at least 4 weeks of active treatment and DLT assessment has been completed.

No BKM120 dose above the recommended single agent dose of 100mg daily will be used.

Based on toxicities, feasibility, and clinical impression the dose level for the expansion cohort will be determined

5.2.2 Dose Escalation Schematic: Dose escalation cohorts and timing for enrollment.

DOSE LEVELS	BKM120 dose	Cetuximab dose
First Dose Level N = 3-6	80mg daily (BKM dose level 0)	500 mg/m^2 administered every 2 weeks (Cetuximab dose level 0)
Second Dose Level N = 3-6	100mg daily (BKM dose level 1)	500 mg/m^2 administered every 2 weeks (Cetuximab dose level 0)
Expansion cohort	MTD or 100mg daily	500 mg/m^2 administered every 2 weeks (Cetuximab dose level 0)

Also see Section 4.1, Table 4-0 for dose levels and dose reductions.

5.2.3 Definition of the Dose-Limiting Toxicity (DLT) for the Dose escalation Phase

DLT is defined as:

(1) Any grade 3 or higher non-hematologic toxicity occurring up to 2 weeks after the last administration of BKM120 and cetuximab, with the following exceptions:

i. Hyperglycemia – to be managed as outlined in Table 4-1

ii. Common cetuximab side effects (rash, hypomagnesemia, infusion reactions) that are manageable as outlined in Tables 4-1 and 4-2

iii. Neuropsychiatric side effects attributed to BKM120 treatment amenable to treatment

iv. Thrombotic events related to indwelling catheters or the underlying cancer

v. Grade 3 diarrhea, nausea, rash, pruritus, and similar events amenable to readily available, and effective treatment such as anti-diarrhea, anti-nauses, anti-rash, and anti-pruritus medications/treatments.

(2) Grade 4 thrombocytopenia, neutropenia, anemia

(3) Intolerable grade 2 and/or intolerable grade ≥ 3 neurospychiatric symptoms

5.3 Design of the Expansion cohort

A total of 18 to 27 patients will be entered into the expansion cohort of the study. **30 patients** in total including both dose escalation and expansion cohorts will be enrolled.

6 Registration Procedures and Data Management

6.1 Guidelines for Lead Institution

All patients should be registered by the responsible Clinical Research Associate and/or Research Nurse in the eVelos Database prior the start of protocol treatment. All selection criteria listed in Section 3.2.2 should be confirmed prior to registration.

6.2 Guidelines for other participating institutions

Eligible participants will be entered on study centrally at the University of Chicago by the Lead Clinical Research Associate. All sites should confirm all selection criteria listed in Section 3.2.2 and then complete the subject Registration Form and call the Coordinating Center at **773-702-2068** or **773-702-2319** or email **adekker@medicine.bsd.uchicago.edu** or **jsteinkamp@medicine.bsd.uchicago.edu** with the following information prior to start of study.

- Provider of information
- Study # and Institution

- Treating Physician
- Patient name/initials and hospital ID number
- Patient's zip code of residence
- Date of signed informed consent
- Gender
- Date of birth of patient
- Diagnosis and date of initial diagnosis
- Anticipated start of treatment

A confirmation of registration will be issued by the lead site upon receipt of the completed registration form.

Participants MUST be registered with the Lead Institution prior to the start of protocol treatment.

6.3 Data collection

Investigators must record the information required by the protocol. Data collection will occur at the University of Chicago using the existing clinical trials infrastructure and clinical trials data management system (eVelos).

7 Statistical methods

7.1 Statistical methods

7.1.1 Criterion for Success/Primary Objectives

- *One week Run-In (randomized):*

  Induction of **compensatory signaling/feedback loop signaling** after one week of BKM120 (run-in) compared to patients not treated with BKM120 (see below for details on measurement and power calculation)

- *Combination treatment:*

  Safety and tolerability of combined treatment with BKM120 and cetuximab

7.1.2 Evaluation of Primary Objectives

- *One week Run-In (randomized):*

Measurement of pEGFR** will be performed using snap frozen tissue samples using the well-established PamGene Kinase array platform available in the Salgia/Seiwert laboratories (also see Section 4.4.4).

The PamGene kinase assay will be performed in triplicates in the initial cases to confirm technical reproducibility. Based on prior experience technical reproducibility is less than one standard deviation (typically 10-15%)*.

The difference in phosphorylation baseline to on-treatment will be calculated and normalized to achieve a near normal distribution of values.

Since the effect size is anticipated to be significant we expect an effect size of at least two standard deviations (see below table for additional considerations including an effect size of 1.5).

We will enroll patients to achieve a minimum of 12 evaluable biopsies (6 per arm), and will aim for 14-18 biopsies as feasible.

Group samples sizes of 6 and 6 achieve 88.9% power to detect a difference of 2 standard deviations between the null hypothesis that both group means are 0 and the alternative hypothesis that the mean of the combination group is 2 with estimated group stand deviations of 1 and 1 and with a significance level (alpha) of 0.05 using a two-sided two-sample t-test.

Should the number of patient biopsies vary power changes accordingly based on a → two-sided two-sample t-test:

Power	N1	N2	Alpha	Beta	Mean1	Mean2	SD1	SD1
85%	9	9	0.05	0.15	0	1.5	≤1*	≤1*
80%	8	8	0.05	0.20	0	1.5	≤1*	≤1*
89%	8	8	0.10	0.11	0	1.5	≤1*	≤1*
94%	7	7	0.05	0.06	0	2	≤1*	≤1*
89%	6	6	0.05	0.11	0	2	≤1*	≤1*
81%	5	5	0.05	0.19	0	2	≤1*	≤1*
82%	4	4	0.10	0.18	0	2	≤1*	≤1*

Based on prior experience technical reproducibility is less than one standard deviation (typically 10-15%).

** While based on preclinical data pEGFR is anticipated to be the most informative marker, the PamGene array platform provides information about other pTyr kinases. In the case that the related marker pHER3 or another marker e.g. pIRS1 are felt to be a more reliable indicators of feedback these markers may be substituted for pEGFR.

- *Combination treatment:*

  Safety and tolerability will be assessed using a 3+3 design as outlined in Section 5. In addition we will perform a descriptive analysis of safety and tolerability for the expansion cohort also. Severe adverse events will be monitored during the entire trial period and in addition to the analysis of the dose expansion phase will be analyzed at the end of the trial for the entire trial cohort.

7.1.3 Evaluation of Secondary Objectives

7.1.3.1 Apoptosis induction

Apoptosis will be measured by TUNEL assay on FFPE sections (using a commercially available kit (e.g. TUNEL apoptosis detection kit (GenScript), or an equivalent method) in a descriptive manner. Since variability is expected to be high, and most patients will not show evidence of apoptosis, the description of the an increase in the rate of apoptosis will be only descriptive. An absolute increase of ≥10% (e.g. 5% → 15%) and relative increase of 33%) will be considered meaningful. In such cases the underlying genotype (PIK3CA mutations etc.) will be reviewed and examined for a possible correlation (descriptive).

7.1.3.2 Response / Tumor Shrinkage

1) Response ≥5 patients respond (RECIST)
2) Induction of responses in patients with prior EGFR failure/ EGFR stability
3) Biomarkers

- Generally agents with a response rate below 5-10% are considered of limited benefit and further development of a single agent is difficult. Alternative approaches such as combination strategies or investigation of subgroups analysis (e.g. gefitinib in HNC) are indicated.
- For HNC a response rate of ≥15-20% would be considered clinically meaningful, especially if responses can be induced in patients with SD or PD while being treated with cetuximab.
- For comparison:
    - Cetuximab response rate is 7-13% (Vermorken et al. 2007; Seiwert et al 2012)
    - We anticipate that ~50% of patients in this study will have been pretreated with cetuximab, or a cetuximab combination. The expected outcome after failure of an EGFR inhibitor is very poor; e.g. in a phase II study of lapatinib in HNC patients previously treated with an EGFR inhibitor no responses were observed and progression free survival was 52 days (de Souza et al. 2012).

→ 1) Secondary efficacy endpoint: Response rate
- P0=0.06 (a poorly effective targeted therapies in the 2nd line setting is estimated to have a response rate of 6% (assuming 7-13% in cetuximab naïve patients and close to 0% in cetuximab resistant patients when treated with single agent cetuximab).
- P1≥0.20 (clinically meaningful alternative response rate)

A sample size of 30 achieves 74% power to detect a difference (P1-P0) of 0.1400 using a one-sided binomial test. The target significant level is 0.0500. The actual significance level achieved by this test is 0.0315. These results assume that the population proportion under null hypothesis is 0.0600.
If the number of responders is 5 or more, the null hypothesis is rejected and drug

called efficacious.

→ 2) Secondary efficacy endpoint: Response rate in patients with prior EGFR failure

The prognosis of patients after EGFR failure is very poor (DeSouza et al 2012). Since there is no established standard of care after EGFR failure and no targeted therapies have proven benefit/activity, response rate in this patient population will be compared to a 0% response rate (DeSouza et al, 2012).

Secondary endpoint: Tumor Shrinkage

Tumor shrinkage will be visualized as a waterfall plot for graphical (qualitative) comparison.

→ 3) Biomarkers

We will also fit logistic and Cox (JRSS, 1972) proportional hazards regression models to examine the effects of laboratory correlates (Biomarker positive group versus biomarker negative group) on response/tumor shrinkage in an exploratory fashion.

7.1.3.3 Overall and Progression free survival

Kaplan-Meier curves will be generated for overall (OS) and progression free survival (PFS) and compared in an exploratory fashion to respective PFS and OS data from a prior study of afatinib and cetuximab as single agents in the recurrent metastatic disease setting (Seiwert et al, 2012) using a logrank test. We will also fit logistic and Cox (JRSS, 1972) proportional hazards regression models to examine the effects of laboratory correlates on PFS, and OS in an exploratory fashion.

7.2 Follow-up trial

As discussed with the study sponsor and depending on data consistent with significant activity the possibility of a follow-up trial or amendment to this trial may be considered.

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8 APPENDICES

8.1 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.

8.2 Appendix B: Tissue Sample Collection Form

BKM120/Cetuximab -- HNC

Clinician/Research Nurse: Please Fill Out

Tissue Samples

Patient Name: _____ MRN# (if applicable): _____

Patient Protocol ID #: _____ Date Tissue Obtained: _____

Institution: _____ Attending Physician:

_____

Site of Biopsy: _____ Site of Primary Tumor: _____

Did Surgical Pathology review tissue for presence of tumor (please circle)? **Yes No**

Number of unstained slides (≥10 slides (5 μm thick), 12-18 ideal):_____

Frozen Sample from biopsy: [ ] Pre-treatment; [ ] Run-in/2nd biopsy; Day:___ after treatment initiation

[ ] 3rd Biopsy

Blood collection (please check):

2 EDTA tubes (purple top, serum), 2x10ml: ___
(e.g. BD#366643 EDTA (K2))

1 SST tube 7.5ml (gold top):_____
(e.g BD#: 367987 SST, 7.5ml)__
(If volume <7.5ml provide add. tube/s)__

Date of blood draw: _____ Time of blood draw:_____

Contact Person's Phone Number/pager/email address:

Dept. of Pathology (University of Chicago)
Tissue Bank Intake Coordinator
5841 S Maryland, MC 3083
Chicago, IL 60637
***Phone* 773-834-8392 or 773-702-0119**

Please notify Dr. Seiwert once the sample was submitted:

Email: **tseiwert@medicine.bsd.uchicago.edu**; or call tissue bank Tel: 773-599-7501