Local Protocol #: 14-008

Title:
A Phase Ib Study of BKM120 with Weekly Cisplatin and Radiotherapy in High Risk Locally Advanced Squamous Cell Cancer of the Head and Neck

Coordinating Center:
Dana Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215

Principal Investigator (PI):
Glenn J. Hanna, MD
Dana Farber Cancer Institute
450 Brookline Avenue
Boston MA 02215
GJHanna@partners.org

Co-Investigators (DFCI):
[redacted]

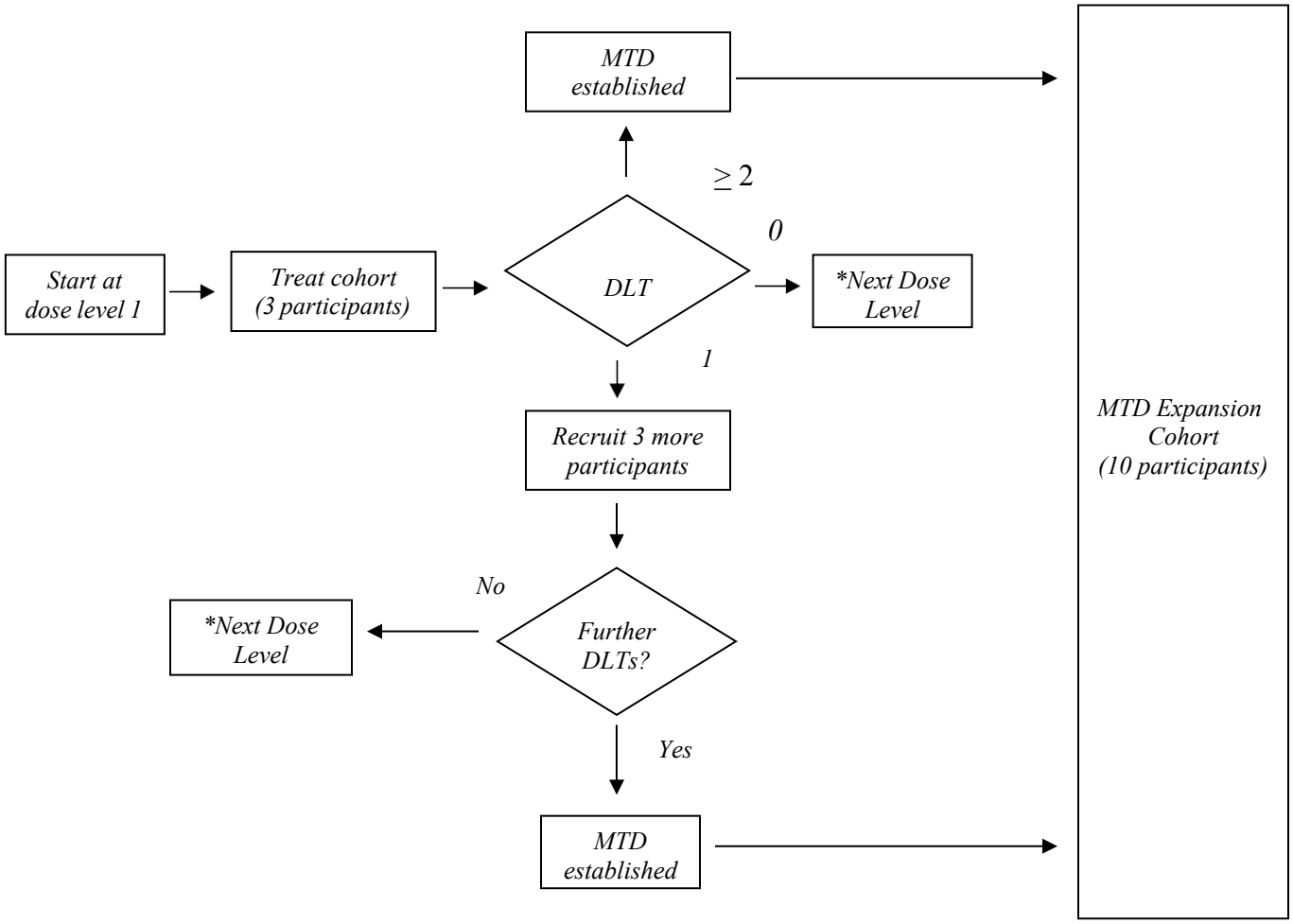
Agent(s):
BKM120, Free Supply, Novartis Pharmaceuticals
Cisplatin, Insurance, Commercial Source

IND #: 121194

IND Sponsor: Glenn J. Hanna, MD

Protocol Type / Version # / Version Date: Version 5 / 31 August 2021

SCHEMA



** If this is the highest dose, then recruit 10 participants to MTD expansion cohort*

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This phase Ib study is combining standard chemoradiotherapy with weekly cisplatin and BKM120 to assess tolerability of this combination in high risk patients with locally advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN). We will also obtain preliminary information about the efficacy of this treatment.

The design of this study follows a classical 3+3 design with a planned expansion cohort of 10 patients when after determination of MTD.

BKM120 will start **2 weeks** prior to first dose of cisplatin and radiation start. Radiotherapy will be standard of care.

Patients will be assessed weekly for adverse events for the duration of the treatment (2 weeks of BKM120 and 7 weeks of CRT = 9 weeks) and every 2 weeks after conclusion of CRT during the first month, then monthly for 3 months, then every 3 months, until first progression , death, or 2 years from study entry whichever occurs first.

Fresh biopsies will be obtained prior to BKM120 and after 7-10d of treatment but prior to start of radiation treatment. Biopsies will be snap frozen and used for correlative studies. Biopsies are optional but encouraged in patients with accessible tumors.

1.2 Primary Objectives

Determine Maximum Tolerated Dose (MTD) of BKM120/cisplatin in combination with radiation therapy in patients with locally advanced squamous cell cancer of the head and neck.

1.3 Secondary Objectives

Assess:

- Overall response rate
- Time to progression
- Survival
- Mood alteration from BKM120
- Activity of BKM120 as single agent in sequential biopsies

2. BACKGROUND

2.1 Study Disease

There are >50 000 new cases of squamous cell cancer of the head and neck in the US annually and it is the fifth leading cause of death among cancer patients (Jemal, et al 2010)

The majority of patients present with potentially curable, locally advanced disease. For most patients, treatment consists of concurrent chemotherapy plus radiation (chemoradiotherapy, CRT). The standard chemotherapy agent used in conjunction over the 7 week radiotherapy course (70 Gy, 35 fractions) is cisplatin which can be given either as a bolus infusion every 3 weeks or weekly. Many oncologists prefer weekly cisplatin because of better tolerability compared to bolus cisplatin and similar efficacy.

The cure rate of locally advanced stage III or IV disease is only around 50% historically and recurrence rates have remained high (Forastiere 2000). The primary risk is loco-regional failure, often within the field of prior radiotherapy. Maximizing efficacy of radiotherapy is therefore critical to improve prognosis.

In recent years, HPV positive squamous cell cancer has been recognized as a clinical entity that is characterized by good response to treatment and excellent prognosis. These patients are typically younger and do not have a history of smoking (Gillison 2010). Trials are under way that target this patient population with the goal of reducing the intensity of treatment and thus the severity of acute and long term side effects. However, these patients represent a minority among the head and neck cancer population. If a significant smoking history (>10 pack years) is present, the prognosis is poor, even in those patients who have HPV positive disease (Ang, et al 2010). Recurrences present primarily as loco-regional failures within the radiation field suggesting resistance to radiation.

Resistance to radiotherapy is complex and poorly understood. Recent data suggest however, that PI3 Kinase/AKT activity is closely connected with three major radioresistance mechanisms: intrinsic radioresistance; tumor-cell proliferation; and hypoxia. Conversely, PI3K inhibition is associated with radiosensitization (Hosoi, et al 1998; Bussink 2008; Nakamura, et al 2005). Furthermore, activation of the PI3K pathway is frequent in head and neck cancer, either through mutations of PI3Kor other components of the PI3K pathway such as mTOR, AKT or PTEN which are present in almost one third of all head and neck squamous cell cancers, but may also occur in response to radiotherapy in cases without mutations along the PI3K pathway (Stransky et al 2011, Lui at a 2013, Toulany et al 2005). HPV positive oropharyngeal cancer, which accounts for a large portion of newly diagnosed patients with locally advanced SCCHN is also frequently associated with activating PI3K mutations. Furthermore, our own data suggest that presence of genetic mutations of the NFE2L2/KEAP1/CUL3 pathway which is present in one-third of patients with HNSCCs may play a particularly significant role and radioresistance could be restored with BKM120 (Abazeed, et al 2013). As a pan-PI3K inhibitor, BKM120 should thus act as an effective radiosensitizer and could help to target a key pathway in SCCHN, thus improving outcomes.

2.2 Study Drug: 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.

2.2.1 PI3K Pathway and mechanism of action

The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso, et al 2001). PI3K signaling also serves a central role in the pathogenesis of

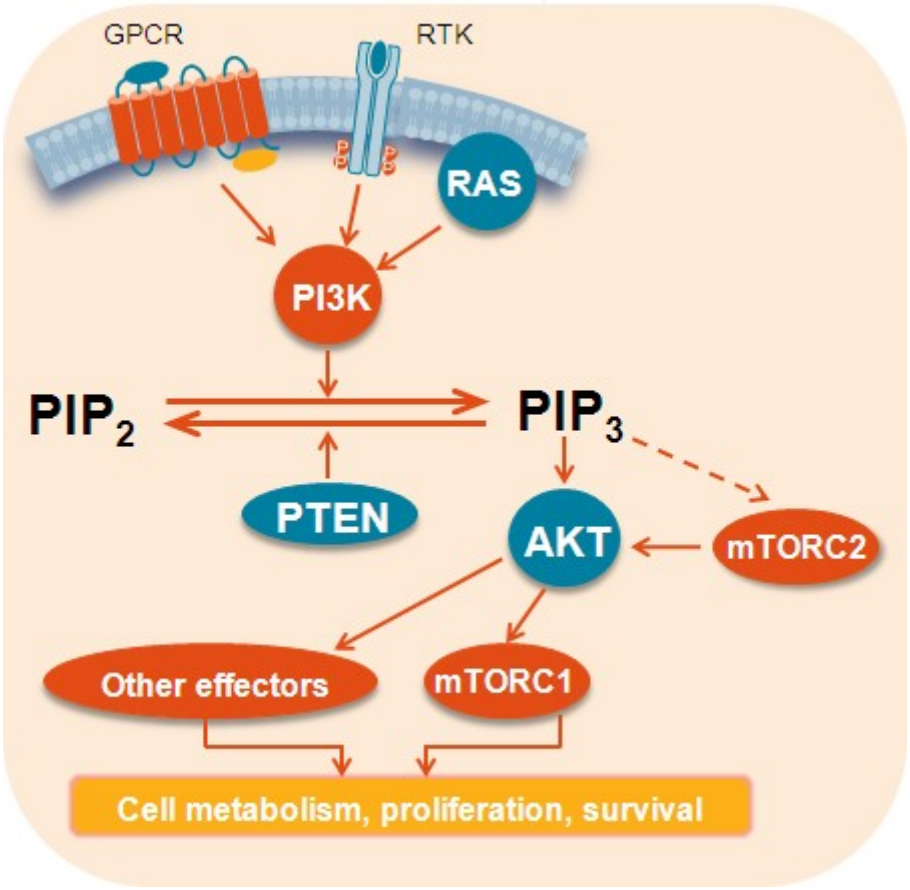
numerous forms of neoplasia. At the structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. The PI3K signaling is modulated by multiple regulators, including growth factors (such as EGF, IGF-1, and FGF), hormones (such as estrogen and thyroid hormone), integrins, intracellular calcium levels, and RAS signaling. PI3K signaling is negatively regulated at the level of PIP3 clearance by phospholipid phosphatases, such as the phosphatase and tensin homologue (PTEN) protein and the inositol 5-phosphatase-2 (SHIP2) protein. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006). Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers. Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to,

a. Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins) or

b. Loss-of-function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g., loss of PTEN expression or function) (Chow 2006, Cully 2006)

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

Figure 1: Schematic representation of the PI3K pathway



2.2.2 Clinical 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.

Table 1: Inhibitory activities (IC50) of BKM120 against other PI3K or related kinases

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

All the IC50s (expressed in µM ± SD) were determined as described in the method report [RD-2007-00365], using a KinaseGlo® (Class I or III PI3Ks, and PI4Kβ) or TR-FRET assay format (mTOR).

BKM120 significantly inhibits p110α and the most common p110α mutations (H1047R, E454K, E542K), p110β, p110δ and p110γ but not the related proteins Vps34, mTOR or PI4Kβ. Hence BKM120 is classified as a pure pan-class I PI3K inhibitor. Enzymatic characterization of the inhibitory properties of the compound revealed that BKM120 is a mixed inhibitor of PI3Kα with a strong competitive component (largest on Vmax). The cocrystal X-ray structure of BKM120 with PI3Kγ confirmed that BKM120 interacts with PI3K into the ATP catalytic cleft. The PI3K pathway regulates the activity of the mTORC1 complex, when cells are challenged through mitogenic stimuli. In order to assess in cells the potential impact of the BKM120 on the mTORC1 complex, the compound was tested in TSC1 null cells. These cells express a constitutively activated mTORC1 complex that uncouples the mTOR pathway from the PI3K upstream input (Kwiatkowski 2003). When exposed to TSC1 null MEFS, BKM120 reduced the S235/236P-RPS6 levels with an IC50 of 1785 nM, in agreement with the data obtained in the mTOR biochemical assay. In contrast, and as expected the allosteric mTORC1 inhibitor RAD001 displayed sub-nanomolar inhibitory activity in this assay. In contrast to molecules with distinct mechanism of action (BCR-Abl inhibitor STI571, mTORC1 allosteric inhibitor RAD001), BKM120 is able to decrease the phosphorylation status of various either direct (GSK3β, FKHRL1/FOXO3a) or indirect downstream Akt effectors (p70S6K, through mTOR) in the PTEN null U87MG cell line, as efficiently as prototypical PI3K inhibitors such as LY294002 and Wortmannin.

2.2.3 Preclinical Safety

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

2.2.4 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-p110cells). 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.

2.2.5 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.

2.2.6 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 formationoccurred 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.

2.2.7 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.

2.2.8 Clinical experience

2.2.8.1 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.

2.2.8.2 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 2.

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

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

A second single agent trial, [CBKM120X1101] was a phase I dose escalation study in Japanese patients with advanced solid tumors with dose levels ranging from 25 to 100mg/day (Doi 2011). Enrolment of 15 patients has been completed, including 9 patients at 100 mg/day. One DLT (G4 hepatic function abnormal) was observed in the 100 mg/day group. The most common G3 or G4 adverse events occurring in at least 2 patients were hepatic function abnormal in 6 patients including transaminase increase in 2 patients, G3 anemia in 2 patients, hypokalemia in 2 patients. The recommended phase 2 dose (RP2D) for Japanese 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 Phase Ib 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.

2.2.8.3 Liver Toxicity

Liver toxicity has been analyzed based on a search of multiple MedDRA event terms and is presented in Table 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 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.

2.2.8.4 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 4).

Table 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.

2.2.8.5 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 15 for more detailed guideline on the diagnosis and management of Pneumonitis.

2.2.8.6 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 5.

Table 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 5.

2.2.8.7 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 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 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.

2.2.8.8 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 combinedwith 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).

2.2.9 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.

2.3 Rationale

Because of the connection with radioresistance and the high rate of mutations along the PI3K pathway in HNSCC, PI3Kinase inhibition should be an excellent strategy to overcome radioresistance and ultimately improve outcomes in LAHNC patients at high risk for loco-regional recurrence who undergo concurrent chemoradiotherapy with curative intent.

We propose a phase Ib study using the combination of BKM120 in combination with standard weekly cisplatin and radiotherapy in patients who are treated for locally advanced disease with curative intent.

We believe that weekly cisplatin dosing at 30mg/m2 is a reasonable standard as a starting dose since over the course of a 7 week chemoradiotherapy regimen, patients receive a total cumulative dose of 210mg/m2, similar to the two standard doses of bolus cisplatin 100mg/m2 each.

A retrospective study comparing chemoradiotherapy with bolus cisplatin (100mg/m2) versus weekly cisplatin (20mg/m2 weekly) failed to demonstrate significant differences in outcome (Kose et al 2011).

A prospective study similarly concluded that weekly cisplatin versus bolus cisplatin (100mg/m2 d 1, 22) was equally effective. The starting dose of 40mg/m2 had to be modified in many cases and the cut-off for successful treatment with cisplatin was a cumulative dose of 200mg/m2 or more (Homma et al 2011).

Even under the unlikely assumption that BKM120 is not active, the starting dose of cisplatin should provide sufficient radiosensitization compared to the standard of care.

3. PARTICIPANT SELECTION

Depending on toxicities encountered during the trial. Up to 46 patients are anticipated to be treated on this protocol.

3.1 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. Patients eligible for enrollment in the treatment phase of this study **must meet all** of the following criteria:

3.2 Inclusion Criteria

1. Patients with stage III/IV per tumor/nodes/metastasis (TNM) guidelines for head and neck sites (American Joint Committee on Cancer [AJCC] 7th Edition), locally advanced, biopsy proven squamous cell cancer of the head and neck that undergo chemoradiation as their primary treatment with curative intent. Patients with oropharynx (HPV positive and HPV negative), hypopharynx, larynx primaries, nasopharynx as well as those with documented SCC of the cervical lymph nodes, with unknown primaries, are eligible.
2. >10 pack years of tobacco use or more
3. Age ≥ 18 years
4. ECOG performance status ≤ 2 (Appendix A)
5. Patients must have at least one site of measurable disease [if applicable] (per RECIST 1.1 for solid tumors or the appropriate disease classification/criteria for the target population)
6. Adequate bone marrow function as shown by: ANC > 1.5 x 109/L, Platelets > 100 x 109/L, Hb >9 g/dL
7. Total calcium (corrected for serum albumin) within normal limits (biphosphonate use for malignant hypercalcemia control is not allowed)
8. Magnesium ≥ the lower limit of normal
9. Potassium within normal limits for the institution.
10. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal range
11. Serum bilirubin within normal range (or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with **well documented** Gilbert Syndrome)
12. Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
13. Serum amylase ≤ ULN
14. Serum lipase ≤ ULN
15. Fasting plasma glucose ≤ 120 mg/dL (6.7 mmol/L)
16. Signed informed consent

17. INR ≤ 2

3.3 Exclusion criteria

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

1. Presence of distant metastatic disease
2. Less than or equal to 10 pack years of tobacco history
3. Patients who have received prior chemotherapy
4. Patients who have received prior radiation to the head and neck or adjacent anatomical site (e.g., upper lobe lung, brain)
5. Patients who have received prior treatment with a P13K inhibitor.
6. Patients with a known hypersensitivity to BKM120 or to its excipients
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:
    - 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 grade 3 anxiety
    - Meets the cut-off score of ≥ 12 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or selects a positive response of "1, 2, or 3" to question number 9 regarding potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)
9. Patients with diarrhea ≥ CTCAE grade 2
10. Patient has active cardiac disease including any of the following:
    - Left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Grated acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc > 480 msec on screening ECG (using the QTcF formula)
    - Angina pectoris that requires the use of anti-anginal medication
    - Ventricular arrhythmias except for benign premature ventricular contractions
    - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
    - Conduction abnormality requiring a pacemaker
    - Valvular disease with document compromise in cardiac function
    - Symptomatic pericarditis
11. Patient has a history of cardiac dysfunction including any of the following:
    - Myocardial infarction 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
13. 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.
14. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BKM120 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with unresolved diarrhea will be excluded as previously indicated
15. Patients who 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 18 for a list of prohibited QT prolonging drugs with risk of Torsades de Pointes.
16. Patients receiving chronic treatment with steroids or another immunosuppressive agent.
    - **Note:** Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed. Patients with previously treated brain metastases, who are on stable low dose corticosteriods treatment (e,g dexamethasone 2 mg/day, prednisolone 10 mg/day) for at least 14 days before start of study treatment are eligible.
17. 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.
18. 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 Appendix B for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).
19. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
20. Patients who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant.
21. Women who are pregnant or breast feeding or adults of reproductive potential not employing an effective method of birth control. Double barrier contraceptives must be used through the trial by both sexes. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment.

    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age

appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [***for US only***: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during treatment and for 4 weeks 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 after stopping treatment and for additional 12 weeks (16 weeks in total after study drug discontinuation) and should not father a child in this period.

- Female partner of male study subject should use highly effective contraception during dosing of any study agent and for 16 weeks after final dose of study therapy.

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

3.4 Inclusion of Women and Minorities

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

3.5 Screening

After consent, patients will undergo screening/baseline testing outlined in table 17. Details of the procedures can be found in section 5.12.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Eligible participants will be registered with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

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

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

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study

coordinator and treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1 Treatment Regimen

The investigational therapy used in the course of this study is BKM120. Treatment with BKM120 starts 2 weeks prior to cisplatin and radiotherapy and continues until the end of radiotherapy.

Study medication will be self-administered by the patients continuously throughout radiation. In order to assure compliance with protocol procedures drug administration will be thoroughly explained to the patients. During the study, BKM120 will be administered orally. It is given every day including weekend days. Administration of BKM120 stops with the end of radiotherapy. If radiation is held due to toxicity, BKM120 and cisplatin will be held as well. If cisplatin is held due to toxicity, BKM120 and radiation will continue. If BKM120 is held due to toxicity, cisplatin and radiation will continue. Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label.

BKM120 will be provided by Novartis Pharmaceuticals free of charge. BKM120 is formulated as capsules for oral administration of 10mg and 50mg strength. Capsules are packaged in bottles. BKM120 capsule cannot be crushed and has to be swallowed. It cannot be given via enteral feeding tube.

If vomiting occurs, no attempt should be made to replace the vomited dose.

5.2 Treatment Assignment

This is a non-randomized study, no treatment assignment is necessary. Patients will be enrolled in cohorts of 3- 6 per dose level. Once the MTD is reached, an additional 10 patients will be treated at that dose level and an amendment will be submitted to OHRS to declare the dose.

5.3 Dose Escalation and Stopping Rules

The dose-limiting toxicity (DLT), as defined in Section 5.5, will be the basis for determining the maximum tolerated dose (MTD). Any subject who receives at least one dose of the study drug (BKM120) will be included in analysis for DLT. Treatment cohorts will be dosed in escalating order, as outlined in Table 8, only after the safety of the previous dose level has been established, or until an MTD has been determined.

Subsequent dose levels will be opened for treatment as follows:

1) Escalation to the subsequent dose level will occur only after all subjects in the previous cohort have completed the full 7-week course of BKM120-CRT and have been evaluated for safety and toxicity. Safety will be evaluated based on the incidence of adverse events (AEs), physical exam findings, and clinical laboratory test results. A review of the safety data for each cohort will be conducted when all of the above data are available. In the event that an MTD is not reached after dose level 5, the study will be considered to have reached a biologically acceptable dose appropriate for Phase II study. Any further dose escalations or de-escalations will require a protocol amendment.

2) Three patients will initially be enrolled at dose level 1. The following rules apply for the advancement to the next dose level and to determine the MTD (see also Table 7). Enrollment may proceed at the higher dose according to the rules after three patients have been treated for the 2 weeks of BKM120 followed by 7 weeks of BKM120+CRT at a given dose level and safety data have been reviewed. The dose will be increased until a DLT is observed in one subject. Dose limiting toxicity is graded according to the National Cancer Institute's CTCAE v4.0 (http://ctep.cancer.gov/forms/CTCAEv4.pdf).

Once a DLT occurs, additional subjects will be added to the cohort until either a second subject experiences a DLT or six subjects are treated at that dose level. If no additional subject experiences a DLT at the trigger dose-level, further dose escalation as outlined in Table 8 will be explored in cohorts of three subjects.

If two or more subjects experience a DLT at a given dose, then three additional subjects will be treated at the next lower dose, unless six subjects have already been treated at that dose.

The maximum tolerated dose is the highest dose studied for which the incidence of DLT is less than 33%. The final cohort of three to six subjects may be expanded to 10 subjects to provide additional safety and pharmacokinetic data.

The decision to enroll subjects in the next higher dose level will be made at the discretion of the principal investigator.

Table 7: Dose Escalation Criteria

Number of Subjects per Cohort with DLT During Treatment Period	**Dose Escalation Decision**
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter 3 more subjects at this dose level. If no additional DLT, proceed to the next dose level. If an additional DLT occurs (i.e. ≥ 2 DLTs/6 subjects), dose

	escalation is stopped and the previous dose level is declared the MTD.
≥ 2	The previous dose level is declared MTD. There is no advancement to higher dose levels.

Table 8: Dose Escalation

Dose level	BKM120 (mg, daily)	Cisplatin (mg/m2, weekly)
-1	20	30
1	40	30
2	40	35
3	40	40
4	60	40
5	80	40
6	100	40

BKM120 will start **2 weeks** prior to first dose of cisplatin and radiation start.

Patients will be assessed weekly for adverse events for the duration of the treatment (2 weeks of BKM120 and 7 weeks of BKM120+CRT = 9 weeks) and every 2 weeks after conclusion of CRT during the first month, then monthly for 3 months, then every 3 months until first progression, death, or 2 years post study entry whichever occurs first.

After establishment of MTD, 10 additional patients will be enrolled at the MTD dose level to gain additional experience with this regimen and dose. If the MTD is not reached, because ≤ 1 DLT is encountered at dose level 6, ten additional patients will be enrolled at this dose level. If there are greater than 2 DLTs at dose level 1, enrollment will continue at dose level –1 with no advancement beyond dose level -1.

5.4 Interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of BKM120 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 9. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0.
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

5.5 Dose-Limiting Toxicity

Toxicity will be assessed using the NCI Common Toxicity Criteria for Adverse Events, version 4.0
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf unless

otherwise specified (e.g., hyperglycemia). A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications, and occurs < 28 days following the last dose of BKM120, and meets any of the criteria listed in Table 9.

Whenever a patient experiences toxicity that fulfills the criteria for a DLT (or a potential DLT), treatment with BKM120 will be interrupted (if not otherwise specified) and the toxicity will be followed up as described in section 5.3. Exceptions are CTCAE grade 2 hyperglycemia and CTCAE grade 2 mood alteration, where BKM120 treatment will be continued under appropriate co-medication. The criteria for dose-limiting toxicities are outlined in Table 9.

Table 9: Criteria for Defining Dose-Limiting Toxicities

TOXICITY	ANY OF THE FOLLOWING CRITERIA
Hematologic [a]	≥ CTCAE grade 3 neutropenia for > 7 consecutive days
	CTCAE grade 3 thrombocytopenia for > 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)
Renal	Serum creatinine ≥ 2.0 x ULN to ≤ 3.0 x ULN for > 7 consecutive days
	> CTCAE grade 3 serum creatinine
Hepatic [b]	Total bilirubin ≥ 2xULN to ≤ 3.0 x ULN for > 7 consecutive days
	> CTCAE grade 3 total bilirubin
	CTCAE grade 3 AST or ALT for > 7 consecutive days
	CTCAE grade 4 AST or ALT
Endocrine	Grade 2 hyperglycemia (confirmed with a repeat FPG within 24 hours) that does not resolve to grade 0 within 14 consecutive days (after initiation of glimepiride, metformin or glibenclamide)
	≥ Grade 3 hyperglycemia (confirmed with a repeat FPG within 24 hours)
Metabolic/Laboratory	CTCAE grade 3 asymptomatic amylase and/or lipase, not reversible to ≤ CTCAE grade 2 for > 7 consecutive days
	CTCAE grade 4 asymptomatic amylase and/or lipase
Pancreatitis	≥ CTCAE grade 2
Cardiac	Cardiac toxicity ≥ CTCAE grade 3 or cardiac event that is symptomatic or requires medical intervention
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥ CTCAE grade 3
Neurotoxicity	≥ 1 CTCAE grade level increase
Mood alteration	CTCAE grade 2 mood alteration that does not resolve to ≤ grade 1 within 14 days despite medical treatment (for Anxiety only, if worsened from baseline)
	≥ CTCAE grade 3 mood alteration
Dermatologic	Any phototoxicity ≥ CTCAE grade 2, or skin toxicity (rash) resulting in interruption of BKM120 for > 21 consecutive days
Other adverse events	≥ CTCAE grade 3 adverse events (excluding ≥ CTCAE grade 3 elevations in

	alkaline phosphatase)
	≥ CTCAE grade 3 vomiting or CTCAE grade 3 nausea despite the use of standard anti-emetics
	≥ CTCAE grade 3 diarrhea despite the use of optimal anti-diarrhea treatments
	CTCAE grade 3 fatigue (asthenia) for > 7 consecutive days CTCAE grade 4 fatigue (asthenia)
[a] ≥ CTCAE grade 3 anemia will not be considered DLT unless judged to be a hemolytic process secondary to study drug. ≥ CTCAE grade 3 lymphopenia will not be considered DLT unless clinically significant. [b] For any grade 3 or 4 hepatic toxicity that does not resolve within 7 days to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor present), an abdominal CT scan has to be performed to assess if it is related to disease progression. A single patient is assumed not to tolerate the dose if he/she experiences at least one DLT. If a lower grade AE leads to a dose interruption of more than 7 doses of BKM120, this AE will be considered as DLT. If the 2nd occurrence of an initially non-dose limiting toxicity (e.g., grade 3 AST that resolved to ≤ grade 1 within 7 days at 1st occurrence) leads to a dose reduction (Section 6) within 28 days of the first dose of BKM120, this will be considered a DLT.	

The investigator must notify the sponsor immediately of any unexpected ≥ CTCAE grade 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, ≥ CTCAE grade 2 adverse events will be reviewed for all patients at the current dose level.

5.6 Follow-up for dose-limiting toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 10, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose, then the patient should be discontinued from the treatment but will only come off study if dead or due to refusal to continue on the study. All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of BKM120.

Table 10: Follow-up for dose-limiting toxicities

TOXICITY	FOLLOW-UP EVALUATION
Hematology	If ≥ CTCAE grade 3 neutropenia or ≥ CTCAE grade 3 thrombocytopenia have been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 neutropenia or ≤ CTCAE grade 1 thrombocytopenia to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization.
Renal	If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization. If [+3] proteinuria, hematuria ≥ CTCAE grade 2 or serum creatinine ≥ 2.0 x ULN has been demonstrated, a 24-hour urine collection for total protein and total creatinine must be repeated at least weekly until either resolution to baseline value or until stabilization. Whenever a measured CrCl is obtained, a serum creatinine should be obtained within ≤ 72 hours of the urine collection.
Hepatic	If total bilirubin ≥ 2 x ULN or ≥ CTCAE grade 3 AST/ALT has been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 (or ≤ grade 2 for AST or ALT, if liver metastasis are present) to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization. Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Metabolic/Laboratory	If amylase and/or lipase ≥ CTCAE grade 3 (> 2 x ULN) has been demonstrated, these parameters must be assessed once at 2 to 4 days and once again at 7 days (± 1 day) and be repeated twice a week until resolution to ≤ CTCAE grade 2 to allow for initiation of re-treatment, and then at least weekly until either resolution to ≤ CTCAE grade 1 or until stabilization. A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase or lipase. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested in addition.
Endocrine (no CTCAE grading; refer to Table 15 for definition of grades)	For details of the follow-up and treatment of ≥ grade 2 hyperglycemia refer to Table 15.

TOXICITY	***FOLLOW-UP EVALUATION***
Cardiac	*Patient who experience QTc prolongation should be followed as per Table 11.* *In addition, patients who experience ECG abnormalities indicative of an ischemic cardiac event, ECGs should be repeated at least twice a week until normalization or stabilization of ECG findings.* If troponin ≥ CTCAE grade 3 has been demonstrated, this parameter must be repeated twice a week until resolution to ≤ CTCAE grade 1 to allow for initiation of re-treatment, and then at least weekly until either resolution or until stabilization.
Neurotoxicity	*Patients who experience neurotoxicity should be followed as per Table 11.*
Mood alteration *≥ grade 2* *Note: For grade 2 Anxiety only, if worsened from baseline*	*For patient who experience ≥ grade 2 mood alteration a psychiatrist must be consulted for diagnosis and determination of most appropriate medical treatment. Patients must be followed twice weekly by patient self-rating mood scale and be seen weekly by the psychiatrist until resolved ≤ grade 1 or baseline (for anxiety).* *Continue to test weekly by mood scale until resolution to baseline or stabilization* *Refer to Table 12 for more details.*
Non-Laboratory ***Rash***	*Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, stabilization of the toxicity, or study treatment completion* *.* *Whenever a rash is diagnosed, the following should be obtained:* • *A paired skin biopsy from both an affected and an unaffected skin area for local histopathology assessment* • *A plasma sample to assess the concentration of BKM120* *For the follow up of skin rash, refer to Table 6*

5.7 Monitoring of BKM120 suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 10, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose, then the patient should be discontinued from study treatment. If the patient requires more than 2 dose reductions, the patient should be discontinued from study treatment. 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 5.12.11 and 5.12.12.

5.8 Agent Administration

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

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

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. If a patient requires a BKM120 dose delay of >14days from the previous dose, the patient must be discontinued from treatment but will only come off study if dead or due to refusal to continue on the study. Patients will only require a 28 day follow up visit after the last dose of BKM120.

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.

5.8.2 Cisplatin Treatment

Commercially available supplies of cisplatin will be used for this study. Preparation instructions can be found in the FDA approved package insert. Cisplatin will be administered per institutional guidelines.

Cisplatin injection is a sterile, aqueous solution, available in 50ml, 100ml, and 200ml, multiple dose vials, each ml containing 1mg of Cisplatin and 9mg sodium chloride in water for injection. HCI and/or sodium hydroxide added to adjust pH to 3.5 to 4.5. It will be given intra-venously (IV) on days: (1, 8, 15, 22, 29, 36 and 43).

If radiation is held, BKM120 and cisplatin will be held as well. Additional weekly chemotherapy treatments may be added to the treatment course if chemo/XRT was held during the course of treatment. Cisplatin should be given only if at least 3 more days of radiotherapy treatment remain. Days of chemotherapy may be changed (+/-) 2 days if unforeseen circumstances require the timing of treatment. Treatment doses are based on body surface area (BSA). The actual body weight will be used for dose calculations as long as the BSA is below 2. For a BSA above 2, the BSA will be capped at 2.

Cisplatin is nephrotoxic and the patients will receive pre-and post treatment hydration according to institutional standards.

Institutional guidelines for highly emetogenic regimens will be followed. Patients will receive a 5HT antagonist for primary prevention of nausea and vomiting and will also receive 8 mg of dexamethasone IV according to institutional standards. The patients may receive a 5HT antagonist and decadron per IV on day 2 and 3 after chemotherapy for delayed nausea at the discretion of the investigator. The concomitant use of aprepitant and BKM120 is not allowed.

- Possible side effects of cisplatin are
    - Hematologic: Neutropenia, anemia, thrombocytopenia
    - Gastrointestinal: Nausea, vomiting
    - Dermatologic: Alopecia
    - Renal: Elevation of blood urea nitrogen (BUN) and Creatinine, hypomagnesemia, hypokalemia, hypocalcemia
    - Neurologic: Peripheral neuropathy, restlessness
    - Allergic reactions
    - Ototoxicity

Cisplatin is a commercially available product that is provided as part of standard of care.

5.9 Radiation

All patients will receive daily radiotherapy with intensity-modulated radiotherapy (IMRT) delivered at DFCI. The prescribed dose will be 70 Gy (gray, SI unit of absorbed radiation) to the primary and nodal gross tumor volume, given in 2 Gy daily fractions for a total of 35 fractions. Other target volumes will be treated to 63 Gy and 56 Gy using differential dosing, as described below. There will be no planned cone downs or field changes. Treatment will be given 5 days per week for 7 weeks; treatment will not be planned to be delivered on Saturday, Sunday or major holidays, as per standard practice. Radiotherapy will be administered according to the general guidelines below.

- **Volume Definitions**-Volumes for all structures must be contoured on each relevant CT slice.

Gross tumor volume (GTV) consists of tumor at the primary site and gross nodal disease. The volumes will be defined based on imaging studies (CT and/or PET), in conjunction with information from clinical examination.

High risk clinical target volume (CTV1) includes volumes of potential tumor extension (adjacent to the primary or nodal GTV) and clinically/radiographically uninvolved nodal volumes at highest risk for microscopic involvement. The required anatomic margin around the GTV and gross nodal disease will be determined on a case-by-case basis by the treating radiation oncologist, limited by appropriate anatomic constraints. For gross nodal disease, CTV1 will include the nodal station where that node is located. In addition, the high risk clinical target volume may also include the complete anatomic nodal levels immediately adjacent to nodal regions that have gross disease.

Low risk clinical target volume (CTV2) includes lymph node regions at lesser risk for nodal involvement.

Planning target volume (PTV) incorporates a margin that accounts for daily set up variation. The planning target volume will be a 0.5 cm expansion of the gross and clinical target volumes. Modification of PTV is allowed at the discretion of the treating radiation oncologist for sparing of normal tissues, or if it is needed to facilitate the planning process, e.g. if the PTV overlaps a critical structure that must be spared. Each CTV will have an individual PTV designed for set-up uncertainty.

- **Avoidance Structures–**The following normal tissue structures will be defined and delineated on all appropriate CT slices:

(a) Spinal cord, brainstem
(b) Expanded Spinal Cord (7 mm expansion around spinal cord)
(c) Right and left parotid glands
(d) Larynx
(e) Oral cavity

- **Avoidance Structures–**For cases in which the nasopharynx or base of skull is the primary target, the following avoidance structures will be added:
(a) Inner ear
(b) Optic nerves
(c) Optic chiasm
(d) Expanded optic nerve and chiasm (2 mm expansion around these structures)
(e) Eyes
(f) Brain

- **Target Dose Prescriptions**. The three target volumes are described in Section 5.8. All will be treated daily over the course of 35 fractions. The prescription point is at isocenter. To accommodate for tissue heterogeneity, density corrections are required, and will be applied to all plans, unless contraindicated, for example, by significant amounts of scatter on the planning CT scan. Doses will be planned as follows:

(a) **GTV** will be treated to a total dose of 70 Gy in 2.0 Gy fractions.
(b) **CTV1** will be treated to a total dose of 63 Gy in 1.8 Gy fractions.
(c) **CTV2** will be treated to a total dose of 56 Gy in 1.6 Gy fractions.

- **PTV coverage**: No more than 20% of the PTV may receive > 110 % of the prescription dose. No more than 3% of the PTV may receive < 95% of the prescription dose. No more than 1cc of tissue outside the PTV may receive > 110% of the prescription dose.

- **Normal Tissue Doses–**The following normal tissue limits are recommended:

(a) **Parotid Glands:** Mean dose of 26 Gy or less.
(b) **Larynx:** Dose to the larynx should be limited to 50 Gy or less. For tumors in sites adjacent to the larynx, priority is given to tumor coverage. In those cases, at a minimum, an attempt will be made to minimize hot spots in the larynx.
(c) **Oral Cavity:** Volume receiving more than 50 Gy will be limited; constraints are similar to those noted above for larynx.
(d) **Spinal Cord:** No segment of the spinal cord should receive more than 46 Gy. The expanded spinal cord should be limited to 56 Gy for small volume.
(e) **Mandible:** Dose to any point should be less than 70 Gy.
(f) **Inner Ear:** Mean dose should be less than 34 Gy, and the maximum dose less than 47 Gy.

Note: In cases with a conflict/overlap between target and normal tissue, target dose considerations should take priority, at the discretion of the treating physician. An exception to this is the spinal cord dose limitations, which takes priority.

- **Treatment Breaks:** There are no planned treatment breaks on this study; any breaks in planned radiotherapy are strongly discouraged. The Radiation Oncology Study Chair, Roy Tishler, will be contacted at 617-632-3591 for interruptions greater than three treatment days. Radiotherapy interruptions will be permitted for unavoidable mechanical malfunction or serious illness requiring hospitalization, such as sepsis, delirium, severe respiratory compromise or hemodynamic instability, at the discretion of the treating physician and Radiation Oncology Chair. Treatment breaks should be as short as possible. The reason for any interruption in treatment must be documented in the treatment chart.

- **Simulation:** At the time of radiation simulation all patients will have a thermoplastic mask fitted for immobilization. This mask will extend from the top of the skull to below the mid clavicle. Bite blocks, dental rolls and other set-up techniques may be used at the discretion of the treating radiation oncologist.

- **Quality Assurance:**

Prior to the first radiation treatment, the standard quality assurance procedures will be followed. The monitor units required to deliver the prescribed dose shall be calculated. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a quality assurance phantom will be done for each patient that will be treated. In addition, film measurements will be taken during the QA period.

On the first day of treatment each patient will have electronic portal images taken, which will be approved by a radiation oncologist prior to delivery of the first treatment, per standard practice.

Weekly Verification portal images will be taken at least once per week and approved by a radiation

oncologist prior to continuation of treatment per standard practice.

- **Isodose Distribution:** All plans will have complete documentation in the patient's chart, including representative CT slices with treatment isodoses. A DVH with all relevant PTV and CTV structures and all normal tissue structures will be generated for each patient and documented in the patient's radiotherapy chart.

- **Treatment Equipment and Delivery:** Treatment will be delivered on the Dana-Farber Varian Clinac 2100EX or Varian TX. 6 MV energy and dynamic multi-leaf collimators will be used to deliver all treatment.

5.10 General Concomitant Medication and Supportive Care Guidelines

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 exceptions described in Appendix B.

5.11 Duration of Therapy

BKM120 will start **2 weeks** prior to first dose of cisplatin and radiation. BMK120+CRT will then last for 7 weeks. Radiotherapy will be standard of care.

5.12 Visit schedule and assessments (see section 10 for schedule and study calendar)

5.12.1 Laboratory evaluations

5.12.1.1 Pregnancy Test

A serum pregnancy test (β-HCG) is required for all women of child-bearing potential at screening, within 72 hours prior to the first dose of BKM120. Note: Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered "of non-childbearing potential". This should be documented appropriately in the patient's medical history. Additional pregnancy tests should be performed as clinically indicated.

5.12.1.2 Hematology

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

5.12.1.3 Coagulation Profile

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

5.12.1.4 Serum chemistry

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

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

5.12.1.5 Urinalysis

Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity) and will be performed at screening visit and EOT visit. A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal. This must be supplemented with laboratory quantification of any potentially relevant abnormalities.

5.12.2 Vital signs

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

5.12.3 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.

5.12.4 Neuropsychiatric assessments

Patient self-rating mood questionnaires for anxiety and depression (PHQ-9, GAD-7).

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.

5.12.5 ECG/ECHO

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

An echocardiogram (ECHO) or MUGA will be performed to assess eligibility.

5.12.6 Dental Evaluation

All subjects must undergo dental evaluation prior to beginning BKM120 CRT. Any dental extractions must be performed to allow for enough time for healing of the extraction sockets, which is typically 7-10 days.

5.12.7 Performance status

ECOG performance status (Appendix A).

5.12.8 Efficacy assessments

Time to progression is measured from date of study entry to first progression, otherwise patients are censored at date last know progression-free.

Overall survival is measured from date of study entry to death. Otherwise patients are censored at date last known alive.

http://ctep.cancer.gov/protocolDevelopment/docs/Recist_Guideline.pdf

5.12.9 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

5.12.10 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.

5.12.11 Adverse events

Tolerability will be assess using the NCI Common Toxicity Criteria for Adverse Events, version 4.0
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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.

5.12.12 Serious adverse events

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event results in inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one

5.12.13 Novartis instructions for rapid notification of serious adverse events

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

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

All events must be reported, by FAX (877-778-9739**), to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence.** This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has started the treatment to 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.

5.12.14 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.

Information for female partners of male study participants

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

Those methods are the following (a+b):

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

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- Oral contraception, injected or implanted hormonal methods are not allowed as BKM120 potentially decreases the effectiveness of hormonal contraceptives.

- Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for 4 weeks (5 T1/2) after stopping treatment and for additional 12 weeks (16 weeks in total after study drug discontinuation) and should not father a child in this period.

- Female partner of male study subject should use highly effective contraception during dosing of any study agent and for 16 weeks after final dose of study therapy.

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

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

5.13 Duration of Follow Up

Follow up (FU) for adverse events will take place every 2 weeks after conclusion of BKM120+CRT (EOT) during the first month, then monthly for 3 months, then every 3 months, until first progression, death, or 2 years from study whichever occurs first. See Study Calendar for full details.

5.14 Criteria for Removal from Study Treatment and/or Study Itself

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 11. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0.
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

The reason for study treatment discontinuation and/or study removal and the date the participant was removed must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

Reasons that a patient may discontinue study treatment and/or 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

A QACT Treatment Ended/Off Study Form should be filled out when a participant completes study treatment and again when the participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, investigators must immediately notify the Overall PI, Glenn Hanna, MD at 617.632.3090 or page at 617.632.3352.

6. DOSING DELAYS/DOSE MODIFICATIONS

Table 11: BKM120 dose level modification guidelines: Criteria for interruption and re-initiation of BKM120 treatment

Recommended Dose Modifications for BKM120	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
No toxicity	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
Grade 3 (ANC < 1.0 – 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN – 75 x 10^9/L) Grade 2 (PLT < 75 – 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

Recommended Dose Modifications for BKM120	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
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**
Grade 2 (> 1.5 – 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	**Omit dose until resolved to ≤ Grade 1, then:** • **If resolved in ≤ 7 days, then maintain dose level** • **If resolved in > 7 days, then ↓ 1 dose level**
Grade 3 (> 3.0 – 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	**Omit dose until resolved to ≤ Grade 1, then:** • **If resolved in ≤ 7 days, ↓ 1 dose level** • **If resolved in > 7 days discontinue patient from study treatment**
Grade 4 (> 10.0 x ULN)	**Omit dose and discontinue patient from study treatment**
AST or ALT	
Grade 1 (> ULN – 3.0 x ULN)	**Maintain dose level with LFTs* monitored as per protocol**
Grade 2 (> 3.0 – 5.0 x ULN) without bilirubin elevation to > 2.0 x ULN	**Omit dose until resolved to ≤ grade 1, then** • **If resolved in ≤ 7 days, then maintain dose level** • **If resolved in > 7 days, then ↓ 1 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**
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**
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	**Discontinue study treatment permanently.**
* LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. **Monitoring** (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT.	
ENDOCRINE/METABOLIC	
Fasting Plasma Glucose (FPG)	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	**Maintain dose level, check FPG every week** • **initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion** • **instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study** • Consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications) • **check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks**

Recommended Dose Modifications for BKM120	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**

Grade 2 (>160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	• If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria) manage as for Grade 3 hyperglycemia (see below).
	• If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2:
	  • maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1
	  • initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if 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 by 1 dose level
	Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks

Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	• Omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 3:
	  • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate
	  • continue to omit BKM120
	  • monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1
	  • If FPG resolves to ≤ Grade 1 in 7 days or less, then re-start BKM120 and ↓ 1 dose level
	  • If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from BKM120
	  • initiate or continue anti-diabetic treatment as appropriate
	  • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study
	  • consider use of oral anti-hyperglycemic therapy such as metformin
	  • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
	For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit BKM120 and following guidance for management of Grade 3 fasting plasma glucose (FPG)

Recommended Dose Modifications for BKM120	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**

Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	• immediately omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. if grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4:
	  • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate
	  • discontinue patient from BKM120
	  • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study
	  • consider use of oral anti-hyperglycemic therapy such as metformin
	  • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated
	For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue BKM120 and following guidance for management of Grade 4 fasting plasma glucose (FPG).

Recommended Dose Modifications for BKM120	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
CARDIAC	
Cardiac – Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 50 – 40%; or 10-20% drop from baseline	**Maintain dose level**
Symptomatic, responsive to intervention, 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**
Refractory or poorly controlled, ejection fraction < 20%	**Omit dose and discontinue patient from BKM120**
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**
Other Cardiac Events	
Grade 1 or 2	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**
Grade 4	**Omit dose and discontinue patient from BKM120**
OTHER	
Mood alteration	
*** See Table 4 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**

Recommended Dose Modifications for BKM120	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
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
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**
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 psychiatric consult regardless of the total questionnaire score**
Rash	
Grade 1	**Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)**
Grade 2	**Maintain dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)**
Grade 3	**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**
Grade 4	**Omit dose and discontinue patient from BKM120**
Fatigue (asthenia)	
Grade 1 or 2	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then:** • **If resolved in ≤ 7 days, maintain dose level** • **If resolved in > 7 days, ↓ 1 dose level**
Grade 4	**Omit dose and discontinue patient from BKM120**
Other non-hematological adverse events	
Grade 1 or 2	**Maintain dose level**
Grade 3	**Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level**
Grade 4	**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**
Pneumonitis	**See Table 15**
**** Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**	

Fasting Plasma Glucose (FPG)	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	Maintain dose level, check FPG every week • initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study • Consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications) • Check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks

Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	• If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria) manage as for Grade 3 hyperglycemia (see below).
	• If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2:
	  • maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1
	  • initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if 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 by 1 dose level
	• Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks

Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	• Omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 3:
	  • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate
	  • continue to omit BKM120
	  • monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1
	  • If FPG resolves to ≤ Grade 1 in 7 days or less, then re-start BKM120 and ↓ 1 dose level
	  • If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from BKM120
	  • initiate or continue anti-diabetic treatment as appropriate
	  • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study
	  • consider use of oral anti-hyperglycemic therapy such as metformin
	  • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
	For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit BKM120 and following guidance for management of Grade 3 fasting plasma glucose (FPG)

Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	• immediately omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. if grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4:
	  • administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate
	  • discontinue patient from BKM120
	  • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study

	• consider use of oral anti-hyperglycemic therapy such as metformin • check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue BKM120 and following guidance for management of Grade 4 fasting plasma glucose (FPG).

If the toxicity is due to BKM120, only BKM120 will be dose reduced by one level according to the following schedule below. If toxicity occurs at BKM120 20 mg level, BKM120 will be held.

Dose Level	**Dose of BKM120 (mg, daily)**
Level E	100
Level D	80
Level C	60
Level B	40
Level A	20

6.1 Cisplatin Dose Adjustments

- Ototoxicity: If hearing loss occurs, analysis of the risk of additional hearing loss versus the potential benefit of continuing cisplatin should be made. An audiogram may be obtained at the investigator's discretion.

- Nephrotoxicity: If, despite adequate hydration, serum creatinine increases to > grade 1 (≥ 1.5 x ULN), creatinine clearance should be recalculated before the next cisplatin dose and subsequent dose reductions will be recommended as follows:

Dose Modification of Cisplatin in Kidney Impairment

Creatinine Clearance (mL/min)*	Cisplatin Dose**
≥ 60	100%
≥ 40 but < 60	50%
< 40	0%

* Creatinine clearance as calculated by Cockgroft-Gault equation.
** Percent dose reduction is calculated from the original dose, not the previous dose. If creatinine clearance recovers, the dose of cisplatin should be re-escalated to the patient's previous dose level as is outlined in the Dose Modification of Cisplatin in Kidney Impairment chart above. There is no maximum limit.

Serum creatinine will be measured weekly within 24 hours of cisplatin dosing.

Dose Modification of Cisplatin Based on ANC

ANC ($x10^9$/L) within 24	Action to be taken

hrs of therapy	
≥ 1.5	Treat at current dose
≥ 1.0, < 1.5	Treat at 75% of cisplatin dose
< 1.0	Hold treatment, and resume therapy at 75% of cisplatin dose at the next weekly therapy planned when ANC ≥ 1.0. If neutropenia requiring further chemotherapy break occurs, cisplatin will be discontinued for the remainder of the therapy, and only BKM120 and radiation will be continued

Dose Modification of Cisplatin Based on Platelet Count

Platelet count within 24 hrs of therapy	Action to be taken
≥100,000	Treat at current dose
< 100,000	Hold treatment, and resume therapy at 75% of cisplatin dose at the next weekly therapy planned when platelets are at or above 100,000. If thrombocytopenia requiring further chemotherapy break occurs, cisplatin will be discontinued for the remainder of the therapy, and only BKM120 and radiation will be continued.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Expected Toxicities

7.1.1 Known Undesirable Side Effects of BKM120

7.1.1.1 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 ≥ 2 should immediately be examined by a psychiatrist and closely followed medically. Medical treatment with mood stabilizers such as SSRIs (sertaline/fluoxetine) may be prescribed as per investigator's discretion and following consultation of a psychiatrist.

Results of the questionnaire will also be reported in the final manuscript as part of toxicity reporting, using descriptive statistics.

7.1.1.2 Management of mood alteration

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 12: 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 13: GAD-7 anxiety scale

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

Column totals: _____ + _____ + _____ + _____

= Total Score _____

Table 14: 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 _____

7.1.1.3 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 11.

7.1.1.4 Management of Hyperglycemia

In addition to the dose modification and hyperglycemia treatment guidelines in Table 5.

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

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

• For each patient, a maximum of 2 dose reductions will be allowed after which the patient should be discontinued from the study. In addition, a patient must discontinue treatment with BKM120, if after treatment is resumed at a lower dose, hyperglycemia recurs at a worse severity.

• For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated in that patient during future treatment 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.

7.1.1.5 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.

7.1.1.6 Management of Cardiac events

At the screening visit a 12-lead electrocardiogram (ECG), and an echocardiogram or MUGA (ECHO/MUGA) will be performed to assess eligibility. Repeat ECGs will be performed at screening and as clinically indicated. An ECHO/MUGA will be repeated at Day 1 of CRT and EOT.

7.1.1.7 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 15 should be followed. Consultation with a pulmonologist is highly recommended for any Pneumonitis case identified during the study.

Table 15: 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 11) until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with BKM120 until recovery to ≤ Grade 1. May restart study treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with BKM120.

Management of Liver Toxicities

Monitoring: **every 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.

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).

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

7.3 For expedited reporting purposes only:

- AEs for the agent that is listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

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

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports

or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

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

8. PHARMACEUTICAL INFORMATION

8.1 BKM120

BKM120 is being developed as a mono hydrochloride salt due to the favorable physicochemical properties such as good stability, high crystallinity and slightly hygroscopic properties. The majority of the *in vivo* PK and pharmacology evaluation was performed using this salt form.

8.1.1 Form

The drug product is a hard gelatin capsule for oral administration (10mg, and 50mg). Both dosage strengths have the same qualitative composition, although they are not proportionally scaled. The capsulesconsist of dry powder blends made using standard excipients of pharmacopoeial quality: mannitol, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate. The 10-mg capsule uses a Size 1 or Size 3 pink opaque capsule shell, the 50 mg capsules uses a Size 1 capsule shell of pink opaque or grey opaque color.

8.1.2 Storage and Stability

Based on the available stability data, BKM120 capsules are not to be stored above 25°C.
The capsules are packaged in high density polyethylene (HDPE) bottles with induction seals and child resistant caps.

The shelf-life period and storage conditions will be continually assessed based on accelerated and long term stability data.

8.1.3 Handling

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

8.1.4 Ordering

BKM capsules will be supplied by Novartis Pharmaceuticals.

8.1.5 **Accountability**

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

8.1.6 **Destruction and Return**

Unused supplies of the agent will be destroyed according to the DFCI Research Pharmacy policy.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

All patients will have pre-treatment tumor tissue collected (fresh or archival) and NexGen sequencing will be performed to assess the mutational landscape in these cases. This will include over 500 cancer relevant genes.

Fresh biopsies will be obtained prior to and after 7-10d of treatment BKM120 alone. These are optional but encouraged in patients with accessible tumor. Biopsies will be snap frozen. Kinome analysis will be carried out in collaboration with the Broad Institute/MIT, Cambridge, MA. In this assay, tyrosine kinases will be isolated from fresh tumor tissue and phosphorylation status will be assessed in a panel of 55 cancer related kinases. This will provide unique insight into how BKM120 blocks PI3K and its downstream effectors. In addition this will also provide information about possible activation of escape mechanisms such as the MAP-kinase pathway. This could help to further elucidate biological efficacy or resistance.

We expect approximately 30% of patients to be eligible and amenable to sequential biopsies.

The correlative studies to investigate the influence of the NFE2L2/KEAP1/CUL3 pathway, are outlined in the attached research proposal (Appendix D), for which we will receive support through an internal DFCI grant mechanism.

9.2 ImmunoProfile

In addition to the correlative laboratory studies explained in the section above, the investigators may choose to use an additional tissue testing methodology known as ImmunoProfile.

ImmunoProfile uses multiplex immunofluorescent staining and imaging. Multiplex technology uses multiple colors to identify different cells and proteins at the same time on the same slide. Once multiplex staining is complete, the Vectra imager is used to acquire an image of the slide/staining for analysis. Image analysis software is then used to determine the number and percentage of cells positive for the selected immuno-regulatory proteins.

The current version of ImmunoProfile tests for 5 different proteins/markers on one slide (i.e., DAPI, a tumor marker, PDL1, CD8, PD-1 and FOXP3). These initial proteins have been selected because they are targets for existing immunotherapies and there are publications supporting their use as predictors of response.

This test is performed in a CLIA certified clinical laboratory under CLIA guidelines for clinical testing. This is a research test and the study results are not released to patient electronic medical records as of the writing of this document.

Detailed Material and Methods

Staining is performed overnight for ~9 hours on BOND RX fully automated stainers (Leica Biosystems). Tissue sections of 5-µm thick FFPE are baked for 3 hours at 60°C before loading into the BOND RX. Slides are deparaffinized (BOND DeWax Solution, Leica Biosystems, Cat. AR9590) and rehydrated with series of graded ethanol to deionized water. Antigen retrieval is performed in BOND Epitope Retrieval Solution 1 (pH 6) or 2 (pH 9), as shown below (ER1, ER2, Leica Biosystems, Cat. AR9961, AR9640) at 95°C. Deparaffinization, rehydration and antigen retrieval are all pre-programmed and executed by the BOND RX. Next, slides are serially stained with primary antibodies, such as anti-CD8 (clone 4B11; Leica, dilution 1:200). Incubation time per primary antibody was 30 minutes. Subsequently, anti-mouse plus anti-rabbit Opal Polymer Horseradish Peroxidase (Opal Polymer HRP Ms + Rb, Akoya Biosciences, Cat. ARH1001EA) is applied as a secondary label with an incubation time of 10 minutes. Signal for antibody complexes is labeled and visualized by their corresponding Opal Fluorophore Reagents (Akoya) by incubating the slides for 10 minutes. Slides are incubated in Spectral DAPI solution (Akoya) for 10 minutes, air dried, and mounted with Prolong Diamond Anti-fade mounting medium (Life Technologies, Cat. P36965) and stored in a light-proof box at 4℃ prior to imaging. The target antigens, antibody clones, dilutions for markers, and antigen retrieval details are listed in Table 16.

Image acquisition is performed using the Vectra Polaris multispectral imaging platform (Vectra Polaris, Akoya Biosciences, Marlborough, MA). Areas with non-tumor or residual normal tissue (i.e. residual lymph node) are excluded from the analysis. Representative regions of interest are chosen by the pathologist, and 3-5 fields of view (FOVs) are acquired at 20x resolution as multispectral images. Cell identification is performed as described previously (Carey et al, Blood 2016). In short, after image capture, the FOVs are spectrally unmixed and then analyzed using supervised machine learning algorithms within Inform 2.4 (Akoya). This image analysis software assigns phenotypes to all cells in the image, based on a combination of immunofluorescence characteristics associated with segmented nuclei (DAPI signal). Each cell-phenotype specific algorithm is based upon an iterative training / test process, whereby a small number of cells (training phase, typically 15-20 cells) are manually selected as being most representative of each phenotype of interest and the algorithm then predicts the phenotype for all remaining cells (testing phase). The pathologist can over-rule the decisions made by the software to improve accuracy, until phenotyping is optimized. Thresholds for "positive" staining and the accuracy of phenotypic algorithms are optimized and confirmed by the pathologist for each case.

Table 16: Target antigens, antibody clones, dilution of markers, and antigen retrieval conditions used for ImmunoProfile staining

Antibody	Clone	Company	Catalog #	Antibody Dilution	Fluor	Fluor Dilution	Antigen Retrieval, Time (min)
CD8	4B11	Leica	NCL-L-CD8-4B11	1:200	Opal 480	1:150	ER1, 20
PD-L1	E1L3N	Cell Signaling	13684	1:300	Opal 520	1:150	ER1, 20
Foxp3	D608R	Cell Signaling	12653	1:100	Opal 570	1:300	ER2, 40
PD-1	EPR4877(2)	Abcam	Ab137132	1:300	Opal 620	1:300	ER1, 20
Cytokeratin	AE1/AE3	Dako	M351529-2	1:100	Opal 690	1:100	ER1, 20

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 3 weeks prior to study entry. Scans and x-rays must be done ≤4 weeks prior to study entry. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next treatment. Assessments must be performed prior to administration of any study agent. During the treatment phase, study assessments and agents should be administered within ± 2 days of the protocol-specified date, unless otherwise noted. Follow up visits must occur within +/- 14 days of the protocol specified date.

Table 17: Evaluation and visit schedule

Examination	Screening/ Baseline	BKM120 alone phase		Chemo (cisplatin) – radiotherapy (CRT)									
Day of treatment	-21	1	8	1	8	15	22	29	36	43	EOT	FU until first progression[10]	After first progression[11]
Informed consent	X												
Medical History	X												
Inclusion/exclusion criteria	X												
Serum Pregnancy Test (within 72 hours of first treatment for WOCBP)	X	as clinically indicated											
Urinalysis	X			X							X		
Vital signs	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	X	X
Performance Status ECOG	X	X	X	X	X	X	X	X	X	X	X	X	
Neuro-psychiatric assessment (self rating mood questionnaire)[1]	X	X	X	X	X	X	X	X	X	X	X	X	
MUGA/ECHO[2]	X			X							X		
12-lead ECG	X												
Dental Evaluation	X												
Chest X-Ray[3]	X			X							X		
Radiological tumor assessment/response assessment [4]	X											X[4]	
Hematology[5]	X	X	X	X	X	X	X	X	X	X	X		
Serum Chemistry[6]	X			X							X		
Coagulation Profile[7]	X			X							X		
Fasting plasma glucose[8]	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[9]		X	X	X	X	X	X	X	X	X	X	X	

Placement of a PEG is highly recommended prior to beginning BKM120 CRT. It is recommended that this procedure be performed prior to beginning BKM120 CRT or within the first two weeks of therapy.

[1] PHQ-9 and GAD-7 questionnaires will be completed until 1 year post treatment

[2] MUGA/ECHO screening, Day 1 of BKM120+CRT and EOT

[3] A Chest X-Ray should be performed for all patients at screening, Day 1 of CRT and EOT

[4] Screening radiological assessments should be performed within 4 weeks prior to study entry. Radiological tumor assessments should subsequently be performed at 3 months post BKM120+CRT. Follow up imaging after the three month assessment will be at the discretion of the treating oncologist and performed when necessary. Imaging modality (PET/ CT or CT) is at the discretion of the treating oncologist.

[5] Hematology - WBC plus differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts, hemoglobin and platelets. Should be performed on screening, before each BKM120 dose; and EOT

[6] Serum chemistry - K+, Na+, Ca++, Mg++, LDH, ALT, AST, total bilirubin (direct and indirect), creatinine, amylase, GGT, lipase, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, phosphorus, uric acid, total cholesterol, HDL, LDL, triglycerides, glucose, urea or BUN, albumin, and total protein are required at baseline and at end of treatment. Subsequent assessments always include K+, Na+, Mg++, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, alkaline phosphatase, bicarbonate, phosphorus, glucose, urea or BUN, albumin, and total protein BUT, lipase, total cholesterol, HDL, LDL, triglycerides should be obtained on Day 1 of CRT and EOT [7] Coagulation - PT or INR, PTT: Day 1 of CRT and EOT

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

[9] Patients will be assessed weekly for adverse events for the duration of the treatment (2 weeks of BKM120 and 7 weeks of BKM120+CRT = 9 weeks) and every 2 weeks after conclusion of BKM120+CRT (EOT) during the first month, then monthly for 3 months, then every 3 months, until first progression, death, or 2 years post study entry whichever occurs first.

[10] Follow up (FU) will take place every 2 weeks after conclusion of BKM120+CRT (EOT) during the first month, then monthly for 3 months, then every 3 months, until first progression, death, or 2 years post study entry whichever occurs first. Follow up visits must occur within +/- 14 days of the protocol specified date.

[11] After first progression, patients will be followed for survival every 3 months until 2 years post study entry.

Biologic Sample Submission:

Sample Type	Screening/Baseline	BKM120 alone phase (7-10 days)
Blood (whole blood with EDTA)	X	
Archived tumor	X	
Fresh Biopsy*	X	X

*optional, but encouraged in patients with accessible tumors.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria (RECIST 1.1)
http://ctep.cancer.gov/protocolDevelopment/docs/Recist_Guideline.pdf

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

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

12.2 Data Safety Monitoring

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

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

13. STATISTICAL CONSIDERATIONS

This trial follows a standard 3+3 phase I design. The primary endpoint is to determine the MTD. Patients will be started at a given dose and escalated according to the information outlined in section 5.3.
The table below gives the probabilities of the dose escalation scheme outlined in section 5.3.

True Rate of DLT	Probability of Escalation
20%	.71
30%	.49
40%	.31
50%	.17
60%	.08

For example, if the true rate of DLT is 20% at a given dose, there is a 71% probability of escalating to a higher dose.

At most, 46 patients are estimated to be accrued. This is based on studying 6 levels of BKM120+Cisplatin (section 5.3) with at most 6 patients per level plus an additional 10 at the MTD (these 10 accrued to ensure that the adverse event rate at the MTD is acceptable). The estimation of adverse events will be based on studying these 10 additional patients. The width of the 90% confidence interval for the estimation of the adverse event rate will be no more than 56%. The monthly accrual rate is estimated to be 2 to 3 patients.

For secondary objectives: best overall response rate will be summarized as a proportion with a corresponding 90% exact confidence interval, the distributions of progression and survival will be estimated using a Kaplan-Meier method with corresponding 90% confidence intervals for the median or time-specific event time, scores from the GAD-7 and the PHQ-9 to assess mood will be summarized across the timepoints of assessment. Several correlative studies are planned to learn more about how BKM120 blocks PIK. NexGen sequencing of the specimens and studies to investigate the influence of the NFE2L2/KEAP1/CUL3 are planned (see sections 9.1 and Appendix D). Given the small sample size of this trial, these studies are exploratory.

14. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. A report is planned to be published in a peer-reviewed journal and that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three years after the end of data collection.

15. REFERENCES

Abazeed ME, Adams DJ, Hurov KE, et al (2013) Integrative radiogenomic profiling of squamous cell lung cancer. Cancer Res.

Ang KK, Harris J, Wheeler R, et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24-35.

Beaulieu JM, Gainetdinov RR, Caron MG (2009) Akt/GSK3 signaling in the action of psychotropic drugs. Pharmacology and Toxicology; 49: 327-47.

Bendell JC, Rodon J, Burris HA, et al (2012) Phase I, Dose-Escalation Study of BKM120, an Oral Pan-Class I PI3K Inhibitor, in Patients With Advanced Solid Tumors. J.Clin.Oncol.; 30 (3):282-290.

Bussink J, van der Kogel AJ, Kaanders JHAM (2008) Activation of the PI3-K/AKT pathway and implications for radioresistance mechanisms in head and neck cancer. The Lancet Oncology 9:288-296.

Chow L, Baker S (2006) PTEN function in normal and neoplastic growth. Cancer Lett. 241(2):184-96. Epub 2006 Jan 18.

Cully M, You H, Levine AJ, et al (2006) Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. Nat Rev Cancer; 6(3):184-92.

Doi T, Ando Y, Bando H, et al (2011) Phase I dose-escalation study of BKM120, an oral panclass I PI3K inhibitor, in Japanese patients with advanced solid tumors. Molecular Cancer Therapeutics: Volume 10, Issue 11 (Supplement 1, Abstract B159).

Forastiere AA (2000) Head and neck cancer: overview of recent developments and future directions. Semin Oncol 27:1-4.

Grana B, Burris HA, Rodon J, et al (2011) Oral PI3 kinase inhibitor BKM120 monotherapy in patients (pts) with advanced solid tumors: An update on safety and efficacy. J Clin Oncol 29: (suppl; abstract/poster 3043).

Gillison M (2010) HPV and its effect on head and neck cancer prognosis. Clin Adv Hematol Oncol 8:680-2.

Homma A, Inamura N, Oridate N, et al (2011) Concomitant weekly cisplatin and radiotherapy for head and neck cancer. Jpn J Clin Oncol 41:980-6.

Hosoi Y, Miyachi H, Matsumoto Y, et al1 (1998) A phosphatidylinositol 3-kinase inhibitor wortmannin induces radioresistant DNA synthesis and sensitizes cells to bleomycin and ionizing radiation. International Journal of Cancer 78:642-647.

Jemal A, Siegel R, Xu J, et al: Cancer statistics (2010) CA Cancer J Clin 60:277-300.

Katso R, Okkenhaug K, Ahmadi K, et al (2001) Cellular function of phosphoinositide 3- kinases: implications for development, homeostasis, and cancer. Cell Dev Biol; 17:615-75.

Kose F, Besen A, Sumbul T, et al (2011) Weekly cisplatin versus standard three-weekly cisplatin in concurrent chemoradiotherapy of head and neck cancer: the Baskent University experience. Asian Pac J Cancer Prev 12:1185-8.

Kwiatkowski DJ (2003) Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. Cancer Biology & Therapy; 2(5):471-6.

Liu P, Cheng H, Roberts TM, et al. (2009) Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. Aug; 8(8):627-44.

Lui VW, Hedberg ML, Li H, et al (2013) Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers. Cancer Discov 3:761-9.

McCubrey JA, Steelman LS, Abrams SL, et al (2006) Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance. Adv Enzyme Regul; 46:249-79.

Nakamura J, Karlsson A, Arvold N, et al (2005) PKB/Akt mediates radiosensitization by the signaling inhibitor LY294002 in human malignant gliomas. Journal of Neuro-Oncology 71:215-222.

Pursche S, Schleyer E, von Bonin M, et al (2008). Influence of enzyme-inducing antiepileptic drugs on trough level of imatinib in glioblastoma patients. Curr Clin Pharmacol. Sep; 3(3):198-203.

Riddle, Rosenstock, and Gerich (2003) The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Nov; 26(11):3080-6.

Rodon J, Bendell JC, Abdul Razak AR, et al (2011) Safety Profile and Clinical Activity of Single-Agent BKM120, a Pan-Class I PI3K Inhibitor, for the Treatment of Patients with Metastatic Breast Carcinoma. SABCS Abstract P3-16-01.

Saura C, Bendell J, Jerusalem G, et al (2011) Phase I/II Study of BKM120 in Combination with Trastuzumab in Patients with HER2 Overexpressing Metastatic Breast Cancer Resistant to Trastuzumab-Containing Therapy. SABCS Abstract PD09-03.

Stransky N, Egloff AM, Tward AD, et al (2011) The mutational landscape of head and neck squamous cell carcinoma. Science 333:1157-60.

Toulany M, Dittmann K, Kruger M, et al (2005) Radioresistance of K-Ras mutated human tumor cells is mediated through EGFR-dependent activation of PI3K-AKT pathway. Radiother Oncol 76:143-50.

Zhou S-F, Liu J-P, Chowbay B (2009) Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metabolism Reviews; 41(2): 89-295.

Carey CD1, Gusenleitner D2, Lipschitz M2, Roemer MGM3, Stack EC4, Gjini E2, Hu X5, Redd R5, Freeman GJ6, Neuberg D5, Hodi FS6, Liu XS5, Shipp MA6, Rodig SJ7. Topological analysis reveals a PD-L1 associated

microenvironmental niche for Reed-Sternberg cells in Hodgkin lymphoma. Blood. 2017 Sep 11. pii: blood-2017-03-770719.

16. APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: 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. See below 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. See below 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 18 below 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 17: 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		

Strong CYP3A inhibitors	**Moderate CYP3A inhibitors**	**Strong CYP3A inducers**	**Moderate CYP3A inducers**
nelfinavir	verapamil		
posaconazole	amprenavir		
ritonavir	fosamprenavir		
saquinavir	elvitegravir		
telithromycin	tipranavir		
troleandomycin			
voriconazole			
This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase BKM120 AUC > 5-fold, and moderate inhibitors are predicted to increase BKM120 AUC ≥ 2-fold but < 5-fold. This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche et al. 2008).			

Table 18: LIST OF PROHIBITED QT PROLONGING DRUGS

All QT-prolonging drugs listed in this table are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 18 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

Drug	**QT risk(*)**	**Comment**
Amiodarone	Known risk for TdP	Females>Males,TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
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

Drug	QT risk(*)	Comment
Haloperidol	Known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate 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.		

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 19 for a list of CYP450 substrates and carefully consider their co-administration with BKM120.

Particularly, caution is advised when BKM120 is co-administered with:

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

- Oral anti-diabetics which are metabolized by CYP2C8 or CYP2C9 can possibly result in hypoglycemia. Patients who develop diabetes mellitus during the study should be treated according to the American Diabetes Association guidance. It is recommended that treatment start with metformin.

- If a patient, after study enrollment, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for torsade de pointes then the investigators, at their discretion, may co-administer such medications. Patients receiving such medications must be monitored. Refer to Table 18 for a list of QT prolonging medications to be used with caution.

Note: please refer also to Table 18 for a list of **prohibited** QT prolonging medication.

- Please refer to Table 19 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 19: 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 20: LIST OF QT PROLONGING DRUGS TO BE USED WITH CAUTION

Drug	**QT risk**	**Comment**
Alfuzosin	possible risk for Torsades de Pointes	
Amantadine	possible risk for Torsades de Pointes	
Amitriptyline	conditional risk for Torsades de Pointes	
Azithromycin	possible risk for Torsades de Pointes	
Chloral hydrate	possible risk for Torsades de Pointes	
Citalopram	conditional risk for Torsades de Pointes	
Clomipramine	conditional risk for Torsades de Pointes	
Clozapine	possible risk for Torsades de Pointes	
Desipramine	conditional risk for Torsades de Pointes	
Diphenhydramine	conditional risk for Torsades de Pointes	

Drug	**QT risk**	**Comment**
Dolasetron	possible risk for Torsades de Pointes	
Doxepin	conditional risk for Torsades de Pointes	
Dronedarone	possible risk for Torsades de Pointes	
Felbamate	possible risk for Torsades de Pointes	
Flecainide	possible risk for Torsades de Pointes	
Fluoxetine	conditional risk for Torsades de Pointes	
Foscarnet	possible risk for Torsades de Pointes	
Fosphenytoin	possible risk for Torsades de Pointes	
Galantamine	conditional risk for Torsades de Pointes	
Gatifloxacin	possible risk for Torsades de Pointes	
Gemifloxacin	possible risk for Torsades de Pointes	
Granisetron	possible risk for Torsades de Pointes	
Imipramine	conditional risk for Torsades de Pointes	
Indapamide	possible risk for Torsades de Pointes	
Isradipine	possible risk for Torsades de Pointes	
Levofloxacin	possible risk for Torsades de Pointes	
Lithium	possible risk for Torsades de Pointes	
Mexiletine	conditional risk for Torsades de Pointes	
Moexipril/HCTZ	possible risk for Torsades de Pointes	
Moxifloxacin	possible risk for Torsades de Pointes	
Nicardipine	possible risk for Torsades de Pointes	
Nortriptyline	conditional risk for Torsades de Pointes	
Octreotide	possible risk for Torsades de Pointes	
Ofloxacin	possible risk for Torsades de Pointes	
Ondansetron	possible risk for Torsades de Pointes	
Oxytocin	possible risk for Torsades de Pointes	
Paliperidone	possible risk for Torsades de Pointes	
Paroxetine	conditional risk for Torsades de Pointes	
Perflutren lipid microspheres	possible risk for Torsades de Pointes	
Protriptyline	conditional risk for Torsades de Pointes	
Ranolazine	possible risk for Torsades de Pointes	
Risperidone	possible risk for Torsades de Pointes	
Roxithromycin*	possible risk for Torsades de Pointes	*not available in the United States
Sertindole	possible risk for Torsades de Pointes	

Drug	**QT risk**	**Comment**
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		

APPENDIX C: RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEMA

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/ Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/ Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	
LIVER	None	Mild lassitude Nausea, dyspepsia	Moderate symptoms Some abnormal liver	Disabling hepatitic insufficiency	Necrosis/ Hepatic coma or encephalopathy	

		Slightly abnormal liver function	function tests Serum albumin normal	Liver function tests grossly abnormal Low albumin Edema or ascites		E
KIDNEY	None	Transient albuminuria No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	Persistent moderate albuminuria (2+) Mild hypertension No related anemia Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (<10g%) Severe renal failure Urea >60 mg% Creatinine >4.0 mg%	Malignant hypertension Uremic coma/Urea >100%	F F E C T S
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation	

Summary of Changes, Protocol Version 2; dated 8/27/2015

Section	Change
10	Table 17: Evaluation and visit schedule, has been revised. • Follow up imaging after the three month assessment will be at the discretion of the treating oncologist and performed when necessary. • Imaging modality (PET/ CT or CT) is at the discretion of the treating oncologist. • A follow-up visit window of +/- 14 days was added.

Summary of Changes, Protocol Version 3; dated 06 Jan 2016

Section	Change
Appendix	Questionnaires: • GAD-7 anxiety and PHQ-9 depression scales translated into Spanish.

Summary of Changes, Protocol Version 4; dated 24 May 2021

Section	Change
9.2	ImmunoProfile • Added tumor testing methodology to further evaluate different proteins and markers
15	References • Added reference to align with the information in the new section 9.2 ImmunoProfile
	• Editorial and administrative updates have made throughout the protocol

Summary of Changes, Protocol Version 5; dated 31 August 2021

Section	Change
Throughout Protocol	• Change in PI name and contact information