Phase II Study of Buparlisib in Metastatic Transitional Cell Carcinoma of the Urothelium

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an open-label phase II study of the pan-class I selective phosphoinositide 3-kinase (PI3K) inhibitor Buparlisib in patients with metastatic urothelial carcinoma which has progressed despite treatment with prior cytotoxic chemotherapy. The purpose of the study design is to evaluate the efficacy and safety of Buparlisib in advanced, refractory disease using 2 month progression free survival as a primary endpoint. Buparlisib will be administered orally once daily. Intra-patient dose reduction may be required depending on the type and severity of individual toxicity encountered. Re-staging imaging studies will be performed after every two cycles of treatment (one cycle=4 weeks). Patients may continue on study as long as they are tolerating therapy and in the absence of disease progression.

	Screening	Cycle 1*		Additional Cycles	Post-treatment/ Withdrawal
		Day 1	Day 15	Day 1	
Clinic Visits	**X**	**X**	**X**	**X**	**X**
Buparlisib**		**X→**	→	→	
Radiological tumor response assessment	**X**			**Every 2 cycles**	

* 1 cycle=28 days

** Buparlisib is taken continuously

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Phase II Cohort

Primary

- To measure the progression free survival (PFS) at 2 months for the pan-class I selective PI3K inhibitor Buparlisib in patients with metastatic urothelial cancer that has progressed on prior cytotoxic chemotherapy.

Secondary

- To determine the response rate as determined by RECIST v1.1 for Buparlisib in patients with progressive metastatic urothelial cancer who have received prior cytotoxic chemotherapy
- To determine overall response rate (ORR) in patients with an activated PI3K pathway
- To evaluate the safety and toxicity of Buparlisib in patients with progressive metastatic urothelial cancer who have received prior cytotoxic chemotherapy
- To assess markers of activated PI3K pathway (*PIK3CA* mutations, *PTEN* mutations, or loss of PTEN expression by IHC) in all pretreatment specimens and to correlate with outcome.

Expansion Cohort

Primary

- To measure the progression free survival (PFS) at 2 months for the pan-class I selective PI3K inhibitor Buparlisib in patients with metastatic urothelial cancer that has progressed on prior cytotoxic chemotherapy and harbors genetic alterations predicted to upregulate the PI3K/AKT/mTOR signaling pathway.

Secondary

- To determine the response rate as determined by RECIST v1.1 for Buparlisib in patients with metastatic urothelial cancer that has progressed on prior cytotoxic chemotherapy and harbors genetic alterations predicted to upregulate the PI3K/AKT/mTOR signaling pathway.
- To evaluate the safety and toxicity of Buparlisib in patients with metastatic urothelial cancer that has progressed on prior cytotoxic chemotherapy.

3.0 BACKGROUND AND RATIONALE

3.1 Buparlisib

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

3.2 PI3K Pathway and mechanism of action

PI3K signaling is a hallmark of many cancers. Subsets of cancers become dependent on PI3K pathway signaling ("pathway addicted", Weinstein and Joe (2008)) as a result of mutations of the *PIK3CA* gene itself or of regulators of PI3K (e.g. PTEN, HER2). As a consequence, pathway mutated tumors are particularly sensitive to PI3K pathway inhibition.

The superfamily of PI3 kinases is characterized by primary sequence homologies within the catalytic domain of these enzymes. Currently, 8 members of this family are known, belonging to three classes (I-III). At the structural level, the enzyme PI3K is composed of a 110 kDa catalytic subunit and an 85 kDa adaptor subunit. PI3K signaling regulates diverse cellular functions, including protein synthesis and glucose metabolism, cell survival and growth, proliferation, cellular resilience and repair, cell migration, and angiogenesis (Katso, et al 2001). PI3K is

negatively regulated at the level of PIP_3 by phospholipid phosphatases, such as the phosphatase and tensin homologue PTEN and the inositol 5′ phosphatase-2 SHIP2. In addition, signaling through the PI3K pathway is modulated by crosstalk with other signals and pathways, including hormones (estrogen, thyroid hormones), vitamins, integrins, intracellular calcium and the Ras-dependent MAPK pathway.

Constitutive activation of PI3K signaling is deemed to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors, and in many tumors the PI3K pathway is constitutively activated. Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers. Several lines of evidence suggest that inhibition of the PI3K signaling pathway might provide benefit for the treatment of many cancers including solid tumors (breast cancer, prostate cancer, glioblastoma multiforme, colon cancer, lung cancer etc.) and tumors of the hematopoetic system (Kim 1994, Ram 1996, Ma 2000, Fry 2001, Roymans 2001, Bachman 2004, Broderick 2004, Samuels 2004, Ohgaki 2005, Zeng 2006).

The molecular changes leading to constitutive activation of the PI3K pathway are diverse and fall into four categories: (1): Gain-of-function mutations of oncogenes encoding positive regulators of PI3K (HER2, EGFR, ras, c-src), including oncogenes coding for components of PI3K itself (*PIK3CA*, which encodes for the p110α catalytic subunit, or *PIK3R1*, the gene coding for the p85 adaptor subunit) (2): Loss-of function mutations or deletions affecting negative regulators of PI3K such as PTEN (Chow 2006, Cully 2006) (3): Mutations of genes encoding downstream effectors of the PI3K signaling cascade (e.g. *PDK1*, *AKT/PKB*, *RPS6KB1*) (4): Mutation of the tumor suppressor p53 (i.e. that regulates PI3K signaling through repression of *PIK3CA*).

3.3 Preclinical Studies

Buparlisib activity against class I PI3K (p110α, -β, -δ and -γ), Class III (Vps34), the class IV related PI3K mTOR, or PI4Kβ was assessed using either a luciferase luminescence (class I or III PI3Ks and PI4Kβ) or a TR-FRET assay (Class IV mTOR). The IC50 in these assays is outlined below in Figure 1-1:

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

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

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

Buparlisib significantly inhibits p110α and the most common p110α mutations (H1047R, E545K, and E542K), p110β, p110δ and p110γ but not the related proteins Vps34, mTOR or PI4Kβ. Hence Buparlisib is classified as a pure pan-class I PI3K inhibitor. Enzymatic characterization of the inhibitory properties of the compound revealed that Buparlisib is a mixed inhibitor of PI3Kα with a strong competitive component (largest on Vmax). The cocrystal X-ray structure of Buparlisib

with PI3Kγ confirmed that Buparlisib interacts with PI3K in 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 Buparlisib 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 PI3K upstream input (Kwiatkowski 2003). When exposed to TSC1 null mouse embryonic fibroblasts (MEFs), Buparlisib 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 mechanisms of action (BCR-Abl inhibitor STI571, mTORC1 allosteric inhibitor RAD001), Buparlisib is able to decrease the phosphorylation status of various either direct (GSK3β, FKHRL1/FOXO3a) or indirect downstream Akt effectors (p70S6K, through mTOR) in the PTEN null U87MG cell line as efficiently as prototypical PI3K inhibitors such as LY294002 and Wortmannin.

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

3.3.1 Preclinical Safety

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted in vitro and in vivo, did not indicate a prominent electrophysiological risk. In the isolated rabbit heart, effects pointing towards a shortened repolarization were seen only at 10 μM. Buparlisib inhibited hERG channel activity significantly at concentrations ≥ 100 μM (IC50: 190 μM). The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, observed in two dog telemetry studies, in the absence of an electrophysiologic effect.

Repeated dose studies of up to 4 weeks of duration were performed in rats and dogs. In rats, clinical pathologic changes as well as histopathologic findings were identified the lymphatic system. Findings included decreases in lymphocyte counts in the peripheral blood, decreases in germinal center development in different lymph nodes, and lymphocytolysis in the thymus. In dogs, similar findings were made. In both species, erythropoiesis was affected, as evidenced by reduced erythrocyte counts, accompanied by bone marrow depression observed in rats. The pancreas was affected by treatment with Buparlisib, particularly in dogs, where acinar cell toxicity was seen in the exocrine pancreas. In addition, in one of the four recovery animals minimal acinar cell atrophy was observed after a four week treatment-free period. In rats, in the 4-week study, no pancreatic toxicity was observed (however, in the 2-week dose range-finding study, at higher

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

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, the pancreas and the liver showed changes which are in concordance with this activity.

After up to 2 weeks of treatment with doses of 0.5 or 2.5 mg/kg/day, dose- and time-dependent fluctuations of neurotransmitters were observed in brain tissue but not in plasma or cerebrospinal fluid. However, in two follow-up studies, where effects of an analogue compound lacking tubulin interaction, or the effect fo brain sampling times were investigated, this effect was not confirmed under comparable buparlisib treatment conditions. Given the disparate results between studies, the effects of buparlisib on glutamate, glutamine, GABA, serotonin, 5HIAA, dopamine, or epinephrine in total brain, plasma, or cerebrospinal fluid of female rats is considered to be uncertain at this time and will require further investigation. Both in vitro and in vivo, Buparlisib elicited a genotoxic potential. While no evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro, a potential for genotoxicity was concluded based on the observation of an aneugenic potential, seen in this latter experiment. In line with this result, Buparlisib treatment resulted in an elevated frequency of micronucleated polychromatic erythrocytes in the bone marrow of rats.

Male reproductive 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 although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles; in addition, an increased incidence of diestrus stage of the estrous cycle was seen. In dogs, there was no effect on female reproductive organs.

Data indicate the absence of a relevant potential for phototoxicity with Buparlisib.

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

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

3.3.2 Pharmacodynamics

Buparlisib inhibits wild-type PI3Kα (IC50: 35 nM), with at least 50-fold selectivity toward protein kinases. The compound is equipotent against somatic PI3Kα mutations (H1047R-, E542K- and E545K-p110α) and is active against the other three PI3K paralogs (PI3Kβ, -γ, -δ; 108 to 348 nM

range). Buparlisib does not significantly inhibit the related kinases mTOR and Vps34, nor does it inhibit other receptors and ion channels profiled (IC50 >10 μM).

Buparlisib reduces the phosphorylation of the direct downstream effector Akt in mechanistic and relevant tumor cell lines (IC50: 93 nM for S473P-Akt in Rat1-p110α cells). This biological activity correlates with inhibition of various Akt downstream signaling pathway components, and with its anti-proliferative activity against a variety of tumor cell lines. Our data suggest that response to Buparlisib in breast cancer cell lines is associated with HER amplification and/or *PIK3CA* mutation. The role of PTEN loss-of-function as a predictor of response seems to be less clear.

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

3.3.3 Preclinical Pharmacology, Pharmacokinetics and Metabolism

Buparlisib was rapidly absorbed with a good oral bioavailability in all animal species tested.

The compound has a moderate plasma CL and Vss. Buparlisib is moderately bound to plasma proteins across all species examined and widely distributed to most tissues in the rat. Drug related radioactivity enters the brain and testes, and has an affinity to melanin containing tissues. No unique, major phase I metabolites were identified in human hepatocytes. Buparlisib and metabolites have a low potential for covalent binding to protein. Buparlisib is neither a substrate for nor an inhibitor of P-glycoprotein (MDR-1) or Multidrug Resistance Related Protein, MRP2. The compound is also not an inhibitor of Breast Cancer Resistance Protein (BCRP).

With respect to potential drug-drug interactions, at 100 mg qd Buparlisib is a weak reversible inhibitor of CYP3A4 (K_i 13.6 μM, I/Ki < 1). Buparlisib also weakly inhibited the CYP2C family (2C8, 2C9 and 2C19) with IC_{50} values ranging from 35-65 μM (34-59 μM unbound). Buparlisib shows no apparent time-dependent inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5. Hepatic oxidative metabolism of Buparlisib was found to be predominantly mediated by CYP3A4 (>80%), with only minor contributions of CYP1A1. Hence, Buparlisib is a sensitive CYP3A4 substrate and there is potential for drug-drug interactions with co-medications that are inhibitors or inducers of CYP3A4. Direct glucuronidation via UGT1A4 is implied as well in buparlisib metabolism but until now its contribution was not quantified in vitro. However, direct glucuronides (CNP320) were observed in urine in the hADME trial up to 10%.

Based on the anticipated large contribution of CYP3A4 in the metabolism of buparlisib, a drug-drug interaction trial was conducted with ritonavir (strong mechanism-based inhibitor) to evaluate the impact of ritonavir on a single 30 mg oral dose of buparlisib (CBKM120C2111). The co-administration of 100 mg bid ritonavir resulted in a 73% increase on geometric mean values of AUCinf and a 19% increase on geometric-mean ratio of the Cmax after a single 30 mg dose of buparlisib. There was no significant change in the time to reach maximum concentration. The mean elimination half-life of buparlisib increased from 53.3 hours to 71.6 hours and its mean

apparent clearance decreased from 5.37 L/h to 3.27 L/h as a consequence of the effect of ritonavir on CYP3A4 enzyme. These outcomes showed that ritonavir had a limited effect on the maximum concentration and caused only a mild increase in the exposure of buparlisib. When translating the results of the study to clinical practice, these data could support a less restrictive approach in the concomitant use of moderate CYP3A4 inhibitors with buparlisib.

An additional study was conducted testing the impact of repeat dose of 4 mg daily dexamethasone on the pharmacokinetics of buparlisib. The study was conducted to assess the potential induction impact of dexamethasone at high dose on CYP3A4 and consequently on buparlisib exposure. Overall, buparlisib PK is marginally impacted by repeated dose of 4 mg daily dexamethasone. The gMean ratio for Cmax and AUC were respectively 1.09 and 0.90. This observation is very likely explained by the limited induction capabilities of a 4 mg dose of dexamethasone on CYP3A4. A single 50 mg oral dose of buparlisib (D1 and 8) along with dexamethasone 4 mg daily orally for 11 days (followed by 4 tapering days) was generally safe and well-tolerated in healthy volunteers.

It is possible that Buparlisib may activate PXR in vivo and induce CYP3A4 at concentrations ≥ 50 µM; however, the absence of time-dependent changes in pharmacokinetics of buparlisib in the relevant therapeutic dose range in humans suggests that this may not be relevant in vivo. Finally, experiments show a potential for buparlisib to induce UGT1A1 at concentrations between 0.5 and 100 uM. The mean maximum free concentration calculated at steady state for the 100 mg qd dose in the study [CBKM120X2101] was 0.671 uM (Cmax, tot=4.20 uM). Therefore a potential induction of UGT1A1 cannot be formally excluded; however, the clinical relevance of observed activation of UGT1A1 activity is unclear.

3.4 Clinical experience

3.4.1 Buparlisib Pharmacokinetics and pharmacodynamics

Pharmacokinetic data observed so far showed that Buparlisib is rapidly absorbed after oral administration with mean peak plasma concentrations (C_{max}) ranging between 0.5 to 4 h post dose (t_{max}). The median t_{max} at the MTD dose (100 mg daily) was about 1 hour. After reaching C_{max}, Buparlisib plasma concentrations decreased in a bi-exponential manner. Apparent total body clearance from plasma (CL/F) was low at ~5.0 L/h, indicating that Buparlisib is a low clearance drug. Buparlisib accumulated ~3-fold in achieving steady-state, consistent with an effective half-life of ~40 h. Steady-state can be expected to be reached after approximately 7-10 days of daily dosing in most patients. Approximate dose-proportional increase in C_{max} and AUC was found in the dose range of 12.5-150 mg. Intersubject variability in C_{max} and AUC differed at each dose level but was relatively low and generally around 40%. Doses of 50 mg/day and above led to steady-state drug exposure (AUC_{0-24}) > 10,000 ng*h/mL, a target efficacious exposure level estimated preclinically.

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

and utilization by the tissues (insulin resistance). Hyperglycemia is considered an "on target" effect of buparlisib and has been commonly observed in patients treated with buparlisib with an incidence ranged between 17.6% and 58.3%. The highest rate of hyperglycemia has been observed in trials conducted in patients with controlled diabetes mellitus and in patients with brain metastases. More information is provided in the Investigator's Brochure.

3.4.2 Clinical experience with Buparlisib

As of 15 September 2013, approximately 1469 patients and healthy volunteers have been enrolled into twenty-two Novartis sponsored clinical studies of buparlisib, including 3 blinded phase II and III studies:

Phase I single agent studies [CBKM120X2101], [CBKM120X1101], [CBKM120Z2102], [CBKM120C2110], [CBKM120C2104], [CBKM120C2106], [CBKM120C2111], and [CBKM120C2101].

Phase II single agent studies [CBKM120C2201] and [CBKM120D2201]

Phase I combination studies [CBKM120B2101], [CBKM120X2107], [CBKM120E2101], [CBEZ235A2118], [CLDE225X2114], [CSTI571X2101], [CMEK162X2101], [CINC424A2104], and [CBEZ235D2101].

Phase II combination study [CBKM120F2202]

Phase III combination studies [CBKM120F2302], [CBKM120F2303]

Among these 1469 patients and healthy volunteers, 781 have received at least one dose of buparlisib treatment, as single agent in 254 patients and 95 subjects in pharmacology studies and in combination in 432 patients. Also, 688 patients are enrolled in ongoing blinded phase III studies. The 5 remaining patients were enrolled but did not receive a dose of buparlisib at the time of the cut-off (1 patient in [CBKM120E2101] study and 4 patients in [CBKM120X2107] study).

In pharmacology studies, 95 subjects have been enrolled including 77 healthy volunteers who received one/two doses buparlisib as single agent or in combination. Forty-six out of 77 healthy volunteers were enrolled in three completed studies: four healthy volunteers received one 100 mg dose in [CBKM120C2102], 27 healthy volunteers received two single doses of 50 mg in [CBKM120C2106] and 15 healthy volunteers received two single doses of 30 mg [CBKM120C2111]. Also, 18 hepatically impaired subjects and 13 healthy volunteers received a single 30 mg dose of buparlisib in the [CBKM120C2104] study. Eighteen healthy volunteers received three single doses of 50 mg buparlisib with three different formulations in [CBKM120C2110] a relative bioavailability study.

As of 15 September 2013, six clinical studies have completed recruitment.

Single Agent

In Phase I single agent trials, a total of eleven dose limiting toxicities (DLTs) were observed, nine in CBKM120X2101 in Caucasian population study, one in CBKM120X1101 in Japanese population study and one in CBKM120Z21101 in Chinese population study. The maximum tolerated dose (MTD) was determined to be 100 mg/day buparlisib in Caucasian, Japanese, and Chinese patient population. The recommended phase II dose (RP2D) was confirmed at 100 mg daily for Caucasian and for

Japanese population and is under evaluation in Chinese population.

Moreover, buparlisib single agent at 100 mg daily has been explored in 2 open-label phase II studies conducted in patients with advanced endometrial carcinoma (CBKM120C2201) and squamous cell advanced NSCLC (CBKM120D2201). The limited anti-tumor activity observed has been considered as insufficient to warrant further investigation as single agent in these two indications.

The pharmacokinetic data reveals that buparlisib single agent is rapidly absorbed after oral administration with a median time to reach maximum concentration (Tmax) between 0.5 and 3 hours at steady-state. The variability in exposure and maximum plasma concentration (Cmax) at steady-state for the maximum tolerated dose (MTD) of 100 mg qd is moderate: 33% and 28% respectively. Buparlisib accumulated in a linear fashion (~3-fold) and reached steady-state after 8 days of treatment. At steady-state the median accumulation half-life was esteimated between 35.7 hours and 58.5 hours, calculated based on an accumulation ratio between 3 and 4-fold.

Combinations

Buparlisib is currently tested in several combinations together with trastuzumab (CBKM120X2107) and paclitaxel alone, with paclitaxel and trastuzumab (CBEZ235A2118) with the MEK inhibitor GSK1120212 in the CBKM120B2101 trial with temozolomide and radiotherapy (BKM120E2101) study, with abiraterone in BEZ235D2101 study, LDE2225 in LDE225X2114 study, with STI571 in CSTI571X2101 study, with MEK162 in CMEK162X2101 study, with INC424 in CINC424A2104 study.

Currently three phase III trials are running in patients with metastatic breast cancer with buparlisib at 100 mg daily in combination with fulvestrant or paclitaxel.

For both doses, the predicted Cmax remained lower than the ones observed with 100 mg daily.

These observed decreases in exposure are currently under investigation. They are thought to be due to a combination of formulation factors and the co-administration of anti-acid treatment which might decrease the bioavailability of buparlisib by increasing the gastric pH. This hypothesis will be further explored in the CBKM120F2202 trial and a specific CP trial is currently being designed to investigate the impact of the proton pump inhibitors.

In Phase I combination trials, one DLT was observed in CBKM120X2107 and the MTD and recommended phase II dose (RP2D) was determined as 100 mg/day of buparlisib in combination with weekly trastuzumab.

In CBKM120B2101 trial, 22 DLTs were observed in 19 patients (buparlisib combined with GSK1120121). The MTD was defined at 70 mg/day in combination with 1.5 mg/day of GSK1120212, and the RP2D was defined at 60 mg/day in combination with 1.5 mg/day of GSK1120212.

Eight DLTs were observed in six patients in the dual combination treatment arms in the BEZ235A2118 study, and the MTD was defined at 100 mg/day in combination with weekly paclitaxel 80 mg/m2 for cycles of 28 days. Four DLTs were observed in seven patients in the triple combination (paclitaxel/trastuzumab/BKM120) treatment arms in the BEZ235A2118 study, and the MTD has not yet been determined. Two DLTs were reported in patients treated with temozolomide (TMZ) and

buparlisib and the dose of buparlisib of 80 gm daily has been selected to be administered with TMZ at 150 mg/m2 and 200 mg/m2 day1-5 every 28 days. In addition, 5 DLTs were reported in patients treated with TMZ concomitantly with radiotherapy and buparlisib in CBKM120E2101 study and the MTD has not yet been defined. In CBEZ236D2101 study, one DLT has been reported in one patient treated with abiraterone and buparlisib at 100 mg. When combined with trastuzumab alone, no change in the pharmacokinetics of either entity was observed.

When combined with paclitaxel alone exposures at the MTD appeared to be lower than the ones observed in the first in human trial CBKM120X2101 by around 25%. Cmax was decreased as well by around 50%. The exposures were partially restored in the triple combination with trastuzumab even though the Cmax remained low.

In GSK1120212 trial, the recommended dose for the MTD established at 70 mg and the recommended dose at 60 mg with 1.5 mg GSK1120212. The predicted exposure for the 100 mg dose, based on the 60 mg dose exposure was 29% lower than the ones observed at 100 mg daily in the first in man trial when they would be comparable for the 70 mg daily dose. For both doses, the predicted Cmax remained lower than the ones observed with 100 mg daily. As of 15-Sep-13, there were eleven cases (twenty-two events) with a fatal outcome reported with a suspected relationship with buparlisib.

In the single agent CBKM120Z2102 study, 1 DLT consisting of grade 3 depression was noted at 80 mg/day. In CBKM120B210 combination therapy with GSK1120212, 22 DLTs were noted in 18 patients including grade 3 stomatitis (1) and grade 3 pneumonitis (1).

Study [CBuparlisibX2101] is a phase I first-in-man dose escalation study of single-agent oral Buparlisib in patients with advanced solid tumors. This study has been completed. 83 patients had been enrolled and treated with at least one dose of Buparlisib. The MTD and RP2D of single-agent oral Buparlisib was defined at 100 mg/day. The median age was 56 (30–78) years, the male/female ratio was 33/50 patients, and the distribution of ECOG performance status of 0/1/2 at baseline was 36/46/1 patients, respectively. As of 12 Nov 12, all patients were discontinued from the study treatment. Reasons for discontinuation were disease progression (65.1% of total enrolled), adverse event (24.1%), withdrawal of consent (4.8%), death (4.8%), and protocol deviation (1.2%). The median duration of exposure to study treatment was 7.3 weeks overall. The median duration of exposure to study treatment at the MTD/RP2D arm was 7.6 weeks.

All patients experienced at least one AE. The most frequent AEs (≥10%), regardless of grade, causality and Buparlisib dose, were nausea (45.8%); decreased appetite (42.2%); asthenia (37.3%); diarrhea (36.1%); hyperglycemia (33.7%), rash (32.5%); constipation (30.1%); fatigue (28.9%); vomiting (26.5%); stomatitis (25.3%); abdominal pain (22.9%); pruritus (20.5%); anxiety (19.3%); depression or pyrexia (16.9% each); dry skin, dyspepsia, or somnolence (15.7% each); mood altered (14.5%); AST increased, dizziness, dyspnea, or transaminases increased (13.3% each); back pain, insomnia, or performance status decreased (12.0% each); and ALT increased, arthralgia, cough, or edema peripheral (10.8% each).

The most common CTCAE grade 3 or 4 AEs (>2%), regardless of causality and Buparlisib dose, were asthenia (12.0%); performance status decreased (9.6%); transaminases increased or hyperglycemia (8.4% each); rash (7.2%); hyperbilirubinaemia or AST increased (4.8% each); ALT increased, abdominal pain, fatigue, pneumonia, or diarrhea (3.6% each); and affective disorder, anxiety, mood altered, glucose tolerance test abnormal, arthralgia, dyspnea, pruritus, or intestinal obstruction (2.4%

each). CTCAE grade 3 or 4 AEs were experienced by 57 (68.7%) patients, and 33 (39.8%) patients experienced at least one CTCAE grade 3 or 4 AE suspected to be study drug related. BuparlisibBuparlisibBuparlisibBuparlisibBuparlisibBuparlisibBuparlisib

Study CBKM120D2201 is a phase II open label two-stage study of orally administered buparlisib in patients with non-small cell lung cancer with activated PI3K pathway. As of 15-Sept-2013, 62 patients have been enrolled and treated with at least one buparlisib dose. The median age of the 62 patients was 64.5 years (range: 39-78), the male/female ratio was 40/22 patients, and the distribution of ECOG performance status of 0/1/2 at baseline was 18/41/3 patients, respectively. As of 15-Sept-2013, 60 patients were discontinued from the study and 2 patients were still ongoing. Reasons for discontinuation were progressive disease (50% of total enrolled), adverse event (27.4%), subject/guardian decision (11.3%), physician decision (3.2%), and death (4.8%). The median duration of exposure to study treatment was 6.9 weeks.

All patients experienced at least one AE. The most frequent AEs (>10%), regardless of grade, causality and buparlisib dose, were decreased appetite and diarrhea (35.5% each); asthenia and nausea (32.3% each); hyperglycemia (30.6%); fatigue (25.8%); rash (24.2%); depression and pruritus (21% each); dyspnea (19.4%); alanine aminotransferase increased, anxiety, cough, and weight decreased (17.7% each); aspartate aminotransferase increased and vomiting (16.1% each); dry skin (14.5%); anemia, constipation, and dysgeusia (12.9% each).

The most common CTCAE grade 3 or 4 AEs (>2%), regardless of causality and buparlisib dose were hyperglycemia (16.1%); asthenia (11.3%); dyspnea, aspartate aminotransferase increased, alanine aminotransferase increased and fatigue (8.1%); pneumonia (6.5%); hyponatremia, depression, and respiratory failure (4.8%); mood altered, anemia, nausea, dehydration, hemoptysis, rash, macular rash, lower respiratory tract infection, and sepsis (3.2% each). CTCAE grade 3 or 4 AEs were experienced by 45 (72.6%) patients, and 32 (51.6%) patients experienced at least one CTCAE grade 3 or 4 AE suspected to be study drug related.

There is evidence indicating that the modulation of AKT/GSK3 signaling pathway may play an important role in the behavior regulation. Psychiatric side effects events have been reported in patients treated with buparlisib and are still under investigation. The current data do not allow the identification of any sign or symptom which could predict patient susceptibility to buparlisib induced psychiatric disorders.

At least one AE (regardless of study drug relationship) belonging to SOC “psychiatric disorders,” which include a broad range of AEs such as depression, anxiety, mood altered, confusional state, affective disorders, insomnia, hallucination, panic disorders, has been reported in approximately 17.6% to 66.7% of patients treated with buparlisib. Overall the incidence of grade 3 and 4 psychiatric events ranged from 0 to 13.2%.

No AE corresponding to mood disorder criteria was reported for 11 patients treated with buparlisib, paclitaxel, and trastuzumab in CBEZ23A2118 study. The frequency of mood disorders thus defined, regardless of study drug relationship, ranged from 0% to 44.4%.

As of 15 Sep 13, approximately 1465 subjects, alone in Novartis sponsored trials, have been exposed to buparlisib, mostly patients with advanced solid tumors, in single-agent and combination studies. The majority fo the reported adverse events (regardless of study drug relationship) were mild or moderate (Grade 1-2) and reversible. Although no formal pooled analysis of all AEs from all clinical trials has been conducted to date, AEs can be described in approximate frequency categories based on review of data currently available from completed and ongoing trials. Most frequent events in single agent

studies (occurring in >20% of patients) include, but may not be limited to: nausea, vomiting, diarrhea, decreased appetite, hyperglycemia, abdominal pain, constipation, asthenia, fatigue, macular-papular rash with or without pruritus, mucosal inflammation including stomatitis, increase in liver transaminases, anxiety and depression. Other frequent events (about 10% of patients) include: anemia, altered mood, confusion, dizziness, headache, insomnia, dry skin, back pain, arthralgia, cough, peripheral edema, dyspepsia, fever, hypokalemia, hyponatremia, hypocalcemia, hypophosphatemia, eosinophilia, increase in blood alkaline phosphatase, lipase increase, dysgeusia, and dyspnea. Less common events (less than 5% of patients) that may nevertheless be medically important include: skin infection, hypersensitivity and allergic reactions, eye effects (such as blurred vision, conjunctivitis), respiratory tract infections, pneumonitis, drug rash with eosinophilia and systemic symptoms (DRESS), renal impairment, leukopenia, sepsis, bleeding including epistaxis, psychotic disorders, visual hallucinations, seizures, peripheral neuropathy, hyper or hypotension, arrhythmia, cataract, photosensitivity reactions, activated PTT prolongation, hepatitis, colitis, and encephalitis. One case of suicide was reported in a patient with advanced lung cancer. Three cases of posterior reversible encephalopathy syndrome (PRES) were reported in patients taking buparlisib in clinical trials. With regards to PRES, patients experiencing severe headache, change in behavior, or reason to believe their blood pressure has increased should inform investigators immediately. The written patient information contains this information.

As of 15 Sep 13, there were twenty-two events (in eleven cases) with a suspected relationship with buparlisib and with a fatal outcome. See IB for details.
Please refer to the Investigator's Brochure for additional information on the available clinical experience with Buparlisib.

3.5 Background and Rationale in Urothelial Carcinoma

3.5.1 Urothelial Carcinoma

Bladder cancer is the fourth most common malignancy in men and the ninth most common in women with an estimated 14,000 disease-related deaths in 2009. Early stage disease can be managed with local therapies, including cystoscopic resection and intravesical therapy, while muscle invasive disease is treated with radical cystectomy and perioperative chemotherapy with curative intent. Most patients with metastatic disease are not cured with current therapies and have a median survival of 14 months. Furthermore, no FDA-approved second-line treatment exists after first-line platinum-based chemotherapy, with conventional cytotoxic therapy resulting in a median progression-free survival of 2-3 months and a median survival of 6-9 months (Gallagher 2008). The dismal prognosis observed in patients with advanced or progressive disease in the setting of traditional cytotoxic therapies underscores the need for novel agents in the treatment of metastatic urothelial cancer.

3.5.2 Rationale for BKM-120 in Urothelial Carcinoma

The PI3K-Akt signal transduction pathway is known to be aberrantly activated in a number of solid tumor malignancies, and a wide spectrum of mutations within multiple members of this pathway have been observed in bladder cancer (Knowles 2010). In select series, mutations of *PIK3CA*, the gene encoding for the catalytic subunit of PI3K, have been detected in up to 25% of urothelial carcinoma samples (Platt 2009). Deletions and mutations of PTEN, a phosphatase protein which negatively regulates the activation of PI3K, are also documented to occur in a significant number of cases (Platt 2009). Akt itself can possess activating mutations, leading to

upregulation of multiple downstream proteins involved in cell cycle progression and inhibition of apoptosis (Askham 2010). Other downstream alterations lead to erroneous pathway stimulation, including mutational inactivation of TSC-1, which results in constitutive activation of the mTOR pathway (Platt 2009). Furthermore, amplification of pathway stimulating molecules and deletion of inhibitory proteins are alternative mechanisms of pathway activation which are also observed. Mutations of upstream receptor tyrosine kinases, such as FGFR3, are known to occur in up to 70% of superficial bladder cancers and approximately 20% of invasive, high grade disease (Kompier 2009). The plenitude of aberrations of the PI3K-Akt pathway speaks to the significant role that this pathway plays in bladder cancer development and progression as well as to the potential for deriving clinical efficacy from inhibition of pathway mediators. At Memorial Sloan-Kettering Cancer Center (MSKCC), we have sequenced 137 high-grade bladder cancers for mutations within *PIK3CA* (Iyer 2010). Seventeen (12%) samples were found to possess point mutations. Other sequenced genes included *TP53*, *HRAS*, and *BRAF*, none of which contained as high a frequency of alterations. Mutations within the tyrosine kinase receptor gene *FGFR3* were detected in 16 (12%) samples with three samples containing both *PIK3CA* and *FGFR3* mutations. These results demonstrate that mutations within the *PIK3CA* gene as well as PI3K pathway stimulating molecules such as FGFR3 represent a significant proportion of the alterations in this set of high-grade bladder tumors and that inhibitors of this pathway may have a clinical impact in patients with urothelial carcinoma.

3.5.3 Rationale for the Study Population

The first-line treatment of patients with metastatic urothelial carcinoma varies and may involve a cisplatin- or carboplatin-based doublet or triplet, the four drug MVAC regimen, or a sequential doublet regimen. Furthermore, many patients with metastatic disease have previously received cytotoxic chemotherapy in the perioperative setting. Given this heterogeneity in prior exposure to chemotherapy, the definition of “second-line” or “third-line” chemotherapy has not been well characterized. As a result, we have designed the eligibility for this protocol based on the number of prior chemotherapeutic agents patients have received rather than the number of “lines” of therapy that have been administered. Second-line chemotherapy trials have typically included patients who have received either 1 or ≥ 1 prior regimen(s). Clinical trials at MSKCC have included a maximum of 4 prior drugs because patients are treated with multiple agents in the community before referral. There are no available data demonstrating that the response proportion in the relapsed setting is linked to the number of prior regimens; for example, sunitinib was identified as an active agent in an MSKCC phase II trial of patients with metastatic urothelial cancer who have received a maximum of 4 prior drugs (Gallagher 2010). This prior treatment inclusion criterion will serve to enhance accrual and likely ultimately provide a more homogenous patient population (e.g., most patients will have been exposed to a platinum agent, gemcitabine, and a taxane at some point in their treatment history). Furthermore, we do not anticipate the response to this targeted agent to be closely linked to the number of prior cytotoxic agents administered. If Buparlisib demonstrates activity in this second-line trial, future trials will include an evaluation of the combination of Buparlisib with chemotherapy in the first- and second-line settings.

3.5.4 Rationale for a PFS Endpoint

Pertinent to discovering new drugs active in urothelial cancers is the concept that identifying clinical benefit should not be limited to response. Some of the newer "targeted therapy" agents approved by the FDA have been approved on the basis of improved progression-free survival (PFS) and not response rate (e.g., sorafenib in renal cell carcinoma with a response rate of

approximately 10% but a major impact in PFS and, eventually, an improvement in survival). This being said, the median progression-free survival for bladder cancer patients treated with chemotherapy is modest at only 2-3 months and response rates are in the 10-20% range. In a second-line trial of weekly paclitaxel in 31 patients with progressive urothelial cancer, the median time to progression was 2.2 months. In an ECOG trial evaluating the epothilone analog BMS-247550 in patients with relapsed urothelial cancer, the median progression-free survival was 2.7 months (95% CI, 1.8, 4.1) (Vaughn 2002; Dreicer 2007). In a recently reported phase 3 randomized second-line trial of vinflunine versus best supportive care, the PFS for patients treated with vinflunine was 3.0 months (95% CI, 2.1, 4.0) (Bellmunt 2009). Novel therapies are desperately needed for these patients and identifying activity in the refractory setting by using PFS is considered an acceptable approach with these new targeted agents.

3.5.4 Rationale for Expansion Cohort

PI3K/Akt/mTOR pathway alterations have been genetically characterized in a panel of 97 high-grade urothelial tumors. Thirty percent of samples harbor alterations predicted to upregulate pathway activation within PIK3CA, PTEN, AKT1, or TSC1. Additionally, FGFR3 amplifications and hotspot activating mutations were found in 15% of samples, the majority of which were mutually exclusive from alterations within other members of the pathway. These results indicate that PI3K/Akt/mTOR pathway activation is a common event in UC with the mechanism of activation including truncation of tumor suppressors such as TSC1 and PTEN as well as amplification and/or mutation of oncogenes such as PIK3CA, FGFR3, and AKT1. Preliminary genetic analysis of tumor samples from 13 patients treated in the Phase II portion of this trial is underway. The tumor from one patient who achieved a prolonged partial response to Buparlisib therapy harbors TSC1 loss while a second patient who experienced primary progression of disease after 2 months of treatment was found to have a tumor with loss of TP53 and CDKN1A but no PI3K/Akt/mTOR pathway alterations. These data strongly suggests that in order to maximize the efficacy of Buparlisib, patients whose tumors contain known activating alterations within the PI3K/Akt/mTOR signaling pathway should selectively be enrolled onto study. Based upon the genetic data from the Phase II cohort, e an expansion cohort has been created which comprises selective enrollment of patients with tumors harbor activating PI3K/Akt/mTOR pathway alterations. Routine prospective genetic screening of patients with both locally advanced and metastatic urothelial carcinoma is currently being performed in all bladder-specific medical oncology clinics at MSKCC. Patients are enrolled onto either the GU tissue collection protocol (IRB #89-076) or the institutional protocol (IRB# 12-245), which allow for genetic analysis through Next Generation sequencing using the standardized MiSeq assay as well as the IMPACT assay. Patients can also opt for commercial mutational analysis through Foundation One. Patients with progressive, metastatic UC whose tumors possess alterations predicted to upregulate PI3K/Akt/mTOR pathway activity will be considered for enrollment onto the expansion cohort.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is an open-label phase II study of the pan-class I selective PI3K inhibitor Buparlisib in

patients with metastatic urothelial carcinoma which has progressed despite treatment with prior cytotoxic chemotherapy. The purpose of the study design is to evaluate the efficacy and safety of Buparlisib in advanced, refractory disease using 2 month progression free survival as a primary endpoint.

In the Phase II study, the planned sample size will be 35 patients. A two stage study design will be utilized with a PFS rate at 8 weeks of less than 60% considered not promising while a PFS rate at 8 weeks of 80% or greater will be considered promising. In stage I of the trial, 13 evaluable patients will be accrued to the study. If 8 or more patients demonstrate progression on imaging after 8 weeks on-study, the study will be terminated early and declared to have a negative result. If 9 or more are progression-free at two months, enrollment will be extended to accrue a total of 35 patients. If 24 or more are progression-free after their two month scan (i.e., after stage 2), the treatment will be considered effective and worthy of further testing.

In the Expansion Cohort, the planned sample size will be 21 patients with genetic alterations upregulating the PI3K/AKT/mTOR pathway. A one-stage study design will be utilized with a PFS rate at 8 weeks of less than 60% considered not promising while a PFS rate at 8 weeks of 85% or greater will be considered promising. If 6 or more patients demonstrate progression on imaging after 8 weeks on-study, the study will be declared to have a negative result. If 16 or more are progression-free at two months, the treatment will be considered effective and worthy of further testing.

4.3 Intervention

Buparlisib will be administered at a dose of 100 mg orally once daily (two 50 mg capsules) continuously. Intra-patient dose reduction may be required depending on the type and severity of the individual toxicity encountered. Re-staging imaging studies will be performed after every two cycles of treatment (one cycle = 4 weeks). Patients may continue on study as long as they are tolerating therapy and are free of disease progression.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Investigational Drug Description

NVP-Buparlisib (Buparlisib) is an oral pan-class I phosphoinositide 3-kinase (PI3K) inhibitor belonging to the 2, 6-dimorpholino pyrimidine derivative family.

The drug product is a hard gelatin capsule for oral administration (10 mg, and 50 mg). Both dosage strengths have the same qualitative composition which consists of dry powder blends made using standard excipients of pharmacopeial quality: mannitol, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate. The 10-mg capsules use a Size 1 or Size 3 pink opaque capsule shell. The 50 mg capsules use a Size 1 capsule shell of pink opaque or gray opaque color.

5.2 2 Drug Dispensing/Administration

Administration will be performed on an outpatient basis. Buparlisib will be dispensed as capsules at the

beginning of each treatment cycle. In case of dose modification, patients will be asked to return all of their previously dispensed medication to the clinic and they will be dispensed new-strength capsules. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Medication labels will comply with US legal requirements and will 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.

Buparlisib will be provided by Novartis formulated as capsules for oral administration, and the standard 100mg dose will be taken as two 50mg capsules.

5.3 3 Storage and Stability

Based on the available stability data, Buparlisib 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.

5.4 Source of Drug

Novartis, Inc. will supply Buparlisib free of charge.

5.5 5 Drug Accountability

All study drug supplies must be kept in a locked room with limited access. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinic, or allow supplies to be used other than directed by this protocol without prior authorization from Novartis.

The pharmacist will maintain a complete drug accountability record for each tablet strength with lot numbers of each drug received, including the number of bottles dispensed to each patient, the dates drug was dispensed, and the daily dose of Buparlisib the patient received. The prescribed dose should also be recorded in the patient's medical records.

At the conclusion of the study, all unused Buparlisib capsules will be returned to Novartis for destruction.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Age ≥ 18 years
- Karnofsky Performance Status (KPS) ≥60%
- Urothelial carcinoma of the bladder, urethra, ureter or renal pelvis, with histologic confirmation at MSKCC. Patients with unresected primary tumors may be enrolled as long as evidence of metastatic disease is also present.
- Patients must have progressive metastatic disease. Progressive disease will be defined as new or progressive lesions on cross-sectional imaging (RECIST Version 1.1).

- Patients must have been previously treated, as defined by the following:
    - Patients must have received treatment with at least one prior cytotoxic chemotherapy agent but not more than four prior cytotoxic chemotherapy agents for urothelial carcinoma. Up to four prior chemotherapy agents are allowed, since conventional chemotherapy ranges from just one drug (e.g., gemcitabine) to regimens that contain four agents (e.g., M-VAC is a four-drug regimen containing methotrexate, vinblastine, doxorubicin, and cisplatin).
    - The prior therapy must have consisted of at least one of the following: cisplatin, carboplatin, paclitaxel, docetaxel, or gemcitabine.
    - The prior cytotoxic agents may have been administered in the perioperative or metastatic setting and may have been administered sequentially (e.g., first-line treatment followed by second-line treatment at time of progression) or as part of a single regimen.
- Patients must have at least one site of measurable disease per RECIST 1.1 criteria that has not been previously irradiated. If the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation.
- Patients enrolling in the Phase II study must have pre-treatment tumor tissue available for PI3K/Akt pathway marker analysis: One paraffin block, frozen curls, or 10 freshly-prepared unstained slides from the most representative single paraffin-embedded tumor tissue block should be submitted. Slides from the primary tumor are preferred. If both the primary and metastatic tumor blocks are available, 10 slides from each of the sites should be submitted. If tissue from the primary tumor is not available, a paraffin block or unstained slides from a metastatic site are acceptable. Fine needle aspirates (FNAs) have insufficient tumor tissue and are not permitted.
- Patients enrolling in the Expansion Cohort must have prior mutational testing demonstrating alterations within the PI3K/Akt/mTOR pathway predicted to result in pathway activation.
- Life expectancy of $\geq$ 12 weeks
- Adequate bone marrow function as shown by: ANC $\geq 1.5 \times 10^9$/L, Platelets $\geq 100 \times 10^9$/L, Hemoglobin >9 g/dL
- Total calcium (corrected for serum albumin) within normal limits (bisphosphonate use for malignant hypercalcemia control is not allowed)
  Corrected Calcium = (0.8 * (Normal Albumin - Pt's Albumin)) + Serum Ca
- Potassium and magnesium within normal limits
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal range [or $\leq$ 3.0 x upper limit of normal (ULN) if liver metastases are present]
- Serum bilirubin within normal range (or $\leq$ 1.5 x ULN if liver metastases are present; or total bilirubin $\leq$ 3.0 x ULN with direct bilirubin within normal range in patients with **well-documented** Gilbert syndrome)
- Serum creatinine $\leq$ 1.5 x ULN or 24-hour clearance $\geq$ 50 mL/min
- INR $\leq$ 2
- Serum amylase and lipase $\leq$ ULN

- Fasting plasma glucose ≤ 120 mg/dL (6.7 mmol/L)
- Ability to swallow oral medication

6.3 Subject Exclusion Criteria

- Patients who have received prior treatment with a P13K inhibitor.
- Patients receiving any other investigational therapies.
- Patients with a known hypersensitivity to Buparlisib or to its excipients
- Patients with untreated brain metastases are excluded. However, patients may participate in this trial if > 4 weeks from completion of therapy (radiation and/or surgery) for CNS metastases, are clinically stable at the time of registration and are not receiving corticosteroid therapy
- Patients with acute or chronic hepatic or renal disease or pancreatitis
- 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)
    - ≥ CTCAE grade 3 anxiety
    - Meet the cut-off score of ≥ 10 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 the potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)
- Patients with diarrhea ≥ CTCAE grade 2 or other impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of Buparlisib (e.g., ulcerative diseases, uncontrolled, nausea, vomiting, malabsorption syndrome, or small bowel resection)
- Patient has active cardiac disease including any of the following:
    - Left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc > 480 msec on screening ECG (using the QTcF formula)
    - 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
- Patients with uncontrolled diabetes mellitus or steroid-induced diabetes mellitus.
- 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 lung volumes, DLCO, O2

saturation at rest on room air should be considered to exclude pneumonitis or pulmonary infiltrates

- Patients who have been treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued
- Patients who are currently receiving treatment with any medication that has the potential 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. Refer to Appendix A for a list of prohibited QT-prolonging medications.
- 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 corticosteroid treatment (e.g., dexamethasone 2 mg/day, prednisolone 10 mg/day) for at least 14 days before start of study treatment are eligible.
- 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.
- 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 A for a list of moderate to strong inhibitors of CYP3A4 (Please note that co-treatment with weak inhibitors of CYP3A4 is allowed).
- Patients who have received chemotherapy or targeted anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, antibodies or mitomycin-C) prior to starting study drug or whose side effects from chemotherapy or targeted anticancer therapy have not recovered to a grade 1 before starting the trial.
- Patients who have received any continuous or intermittent small molecule therapeutics (excluding monoclonal antibodies) ≤ 5 effective half lives prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug, patients who have not recovered from side effects of any major surgery, or patients who may require major surgery during the course of the study
- Patients who are currently taking therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulant.
- Women who are pregnant or breast feeding or adults of child-bearing potential not employing an effective method of birth control. Women of child-bearing potential, defined in Section 11.7 (Reproductive Risks), must have a negative serum pregnancy test ≤ 48 hours prior to initiating treatment. Effective methods of birth control are defined in Section #11.7.
- Known diagnosis of human immunodeficiency virus (HIV) infection

- History of another malignancy within 3 years, except non-melanoma skin cancer, excised carcinoma in situ of the cervix, or adenocarcinoma of the prostate that has been surgically treated with a post-treatment PSA that is non-detectable
- Patients who are unwilling or unable to abide by the study protocol or cooperate fully with the investigator

7.1 RECRUITMENT PLAN

Patients will be recruited from the outpatient clinics of the Genitourinary Oncology Service at MSKCC. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team. If the investigator is a member of the treatment team, s/he will screen their patients' medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The patient's initial conversation with the investigator/research staff and portions of the patient's MSKCC medical records will be used to confirm that the patient is eligible for study participation.

8.1 PRETREATMENT EVALUATION

The following will be completed within 14 days prior to initiation of treatment (unless otherwise indicated):

- **Vital signs**
  Vital sign assessment consists of height, pulse, blood pressure, respiration rate, temperature and weight.
- **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), including a skin rash assessment.
- **Performance status**
  Performance status will be assessed at screening and per the visit schedule using the Karnofsky performance status.
- **Pregnancy Test**
  A serum pregnancy test (β-HCG) is required for all women of child-bearing potential (WOCBP) at screening, within 48 hours prior to the first dose of Buparlisib.
- **Hematology**
  Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell (RBCs), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count.
- **Coagulation Profile**
  The coagulation profile includes prothrombin time (PT) or INR, and activated partial thromboplastin time (PTT).
- **Serum Chemistry**
  Serum Chemistry includes the following parameters:

- Comprehensive metabolic panel with conjugated bilirubin (*urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, glucose, bicarbonate, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase (fractionated if grade 2 or higher elevation), AST (SGOT), ALT (SGPT))*
- Lipid Panel *(total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides)*
- Phosphorus
- Uric acid
- Lactic dehydrogenase (LDH)

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

- **Screening tests**
  The additional screening tests include:
  - Magnesium
  - Amylase and lipase
  - Gamma glutamyl transpeptidase (GGT)

- **Urinalysis**
  Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/hpf, RBC/hpf, and any additional findings) exam need only be performed if the urinalysis result is abnormal.
  This must be supplemented with laboratory quantification of any potentially relevant abnormalities.
- **Neuropsychiatric assessments**
  Patient self-rating mood questionnaires for anxiety and depression (PHQ-9, GAD-7) will be conducted during screening. Patients must be below the cutoff scores in either of these questionnaires to be eligible for the trial (see Exclusion Criteria for further details). Please see sections 10.0 and 11.1 for more information regarding neuropsychiatric assessments during treatment.

The following will be completed within 30 days prior to initiation of treatment (unless otherwise indicated):

- **ECG**
  A standard 12 lead ECG is to be performed at screening and significant findings must be recorded.
- **ECHO/MUGA**
  An echocardiogram or MUGA will be performed at screening to assess eligibility
- **Chest X-ray**
  A CT of chest may be performed instead if clinically relevant.
- **Radiological tumor assessment**
  Baseline abdominal and pelvic CT scan and/or MRI of the abdomen and pelvis for abdominal or pelvic indicator lesions
- **Bone Scan**
  In patients with osseous lesions, bone X-rays and/or bone scans should be obtained.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Buparlisib Administration

The study drug Buparlisib 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. Buparlisib will be administered orally on a continuous once daily dosing schedule of 100 mg (two 50 mg capsules) continuously from study day 1 until progression of disease or unacceptable toxicity. Patients should be instructed to take the dose of Buparlisib daily in the morning, one hour after a light breakfast (morning meal) at approximately the same time each day. Buparlisib should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the capsules as a whole and not chew or crush them. Patients should continue to fast for 2 hours following the administration of each Buparlisib dose.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted as an adverse event.

If the patient forgets to take her/his dose before 6:00 PM, then the dose should be withheld that day and Buparlisib 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 Buparlisib dose delay of > 21 days from the previous dose, the patient must be discontinued from treatment completely and will only require a 28 day follow up visit for study completion.

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

9.2 Interruption or Discontinuation of Treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of Buparlisib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 2. Drug may also be interrupted per investigator's discretion if clinically warranted. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0, http://ctep.cancer.gov/protocol Development/electronic applications/docs/ctcaev4.pdf).

Table 1-0 Buparlisib dose level modification guidelines

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

* Starting Dose

9.3 Monitoring of Adverse Events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory tests, or other means will be collected, 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 (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.

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 2, at least once a week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 21 days from the previous dose, then the patient should be discontinued from the study. If the patient requires more than 2 dose reductions, the patient should be discontinued from the study (i.e., patients cannot be treated below dose level -2). All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of Buparlisib. All SAEs must be reported to Novartis as detailed in section 17.2.

Table 2 Criteria for dose-modification in case of suspected Buparlisib toxicity and re-initiation of Buparlisib treatment

Toxicity	Actions
Non-Hematological Toxicity	
Mood Alterations	
** 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* Buparlisib should be omitted for any patient who requires initiation of mood stabilizers for control of mood alteration until their mood alteration has resolved to ≤ Grade 1.	
Grade 1 (or Grade 2 anxiety if present at baseline)	Maintain dose level *Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score*
Grade 2 (for Anxiety only, if worsened from baseline)	Institute appropriate co-medication after consultation with the psychiatrist. • If the condition requires > 14 days for resolution to ≤Grade 1 despite medical treatment, Buparlisib dose should be reduced by 1 dose level. *Note: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score*
Grade 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*
Neurotoxicity	
≥ 1 CTCAE grade level increase	Interrupt BKM until resolved to ≤ grade 1, then resume Buparlisib at one lower dose level
≥ Grade 3	Discontinue Buparlisib
Pneumonitis	
Grade 1	• CT scans with lung windows. Repeat at least every 8 weeks until return to within normal limits. • Maintain dose level
Grade 2	• CT scan with lung windows. Consider pulmonary function testing including: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every three cycles until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL. • Consider corticosteroids if symptoms are troublesome. • Reduce Buparlisib dose by 1 dose level (see Table 1) 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 including: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every two cycles 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 Buparlisib 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 including: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every two cycles 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. • Discontinue treatment with Buparlisib.
Endocrine/Metabolic	
Fasting Plasma Glucose Elevation	
≥ 120 mg/dL - 160 mg/dL	First Occurrence: Maintain dose level Second Occurrence: Maintain dose level, check Fasting Plasma Glucose (FPG) every week • Initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion • Instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study • Check FPG weekly for 8 weeks, then continue checking every 2 weeks
Grade 2 (>160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	First Occurrence: Maintain dose, re-check FPG within 48 hours, and if no worse than Grade 2*: • Maintain dose level • Initiate or intensify medication with appropriate anti-diabetic treatment • Instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study If FPG does not resolve to ≤ Grade 1 within 14 days after initiation/intensifying anti-diabetic treatment: omit Buparlisib • monitor FPG at least weekly until FPG resolves to ≤ Grade 1 • then re-start Buparlisib and ↓ by 1 dose level • continue with anti-diabetic treatment • check FPG weekly for 8 weeks, then continue checking every 2 weeks * If grade "worsens" then follow specific grade recommendations
Grade 2 (>160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	Second Occurrence: Maintain dose, re-check FPG within 48 hours, and if no worse than Grade 2*: • Omit Buparlisib • Initiate or intensify medication with appropriate anti-diabetic treatment • Monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 • Then re-start Buparlisib and ↓ by 1 dose level • Continue with anti-diabetic treatment • Check FPG weekly for 8 weeks, then continue checking every 2 weeks

	* If grade "worsens" then follow specific grade recommendations
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	First Occurrence: Immediately omit Buparlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 48 hours, and if no worse than Grade 3*: • Continue to omit Buparlisib • Monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 • Stop or reduce insulin medication • Then re-start Buparlisib and ↓ by 1 dose level • Continue with anti-diabetic treatment as appropriate • Instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study • Check FPG weekly for 8 weeks, then continue checking every 2 weeks Second Occurrence: Same process as for first occurance, however at the second re-initiation Buparlisib must be dose-reduced a second time. * If grade "worsens" then follow specific grade recommendations
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	Immediately omit Buparlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 48 hours, if confirmed Grade 4: • discontinue patient from Buparlisib • instruct patient to follow dietary guidelines provided by the American Diabetes Association during the study • check FPG weekly for 8 weeks, then continue checking every 2 weeks
Asymptomatic Amylase and/or Lipase Elevation	
Grade 3 (> 2.0 – 5.0 x ULN)	Interrupt until resolved to ≤ grade 2, then: • If resolution to grade ≤ 1 in ≤ 7 days, resume Buparlisib at the current dose level; • If resolution to grade ≤ 1 in > 7 days, resume Buparlisib at one lower dose level
Grade 4 (> 5.0 x ULN)	Discontinue Buparlisib
Renal	
Serum Creatinine	
Grade 2 (> 1.5 – 3 x ULN)	Interrupt treatment until resolution to ≤ grade 1, then : • If resolved to ≤ grade 1 in ≤ 7 days, resume Buparlisib at the current dose level • If resolution to ≤ grade 1 takes > 7 days, resume Buparlisib decreased by one dose level
Grade 3 (>3.0 – 6.0 x ULN)	Discontinue Buparlisib
Grade 4 (> 6.0 x ULN)	Discontinue Buparlisib
Hepatic	
In case of any occurrence of ALT/ AST/ bilirubin increase ≥ grade 2, the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1. Furthermore, for all patients who have experienced ALT/ AST/ bilirubin increase ≥ grade 3 during the study treatment, the monitoring should be continued 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. 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.	
Bilirubin (For patients with Gilbert syndrome, these dose modifications apply to changes in direct bilirubin only)	

Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤3.0 x ULN	Omit 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 • See above for monitoring parameters
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 • See above for monitoring parameters
Grade 4 (> 10.0 x ULN)	Omit dose and discontinue patient from study treatment. See above for monitoring parameters.
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 • See above for monitoring parameters
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 • See above for monitoring parameters
Grade 4 (> 20.0 x ULN)	Omit dose until resolved to ≤ Grade 1 , then ↓ 1 dose level See above for monitoring parameters.
AST or ALT and concurrent bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue study treatment permanently
Monitoring for patients with Gilbert syndrome includes the above LFTs and total and direct bilirubin. Intensified monitoring applies to changes in direct bilirubin only for these patients.	
Gastrointestinal	
Diarrhea	
Grade 2 (4-6 stools/day > pretx)	If diarrhea can be controlled with optimal anti-diarrheal treatment, continue Buparlisib. If not, interrupt treatment until resolved to ≤ grade 1, then resume Buparlisib at the current dose. If diarrhea returns as ≥ grade 2, then interrupt treatment until resolved to ≤ grade 1, then resume Buparlisib at one lower dose.
Grade 3 (7-9 stools/day > pretx)	If diarrhea can be controlled with optimal anti-diarrheal treatment, continue Buparlisib. If not, for diarrhea ≥ grade 3, interrupt treatment until resolved to ≤ grade 1, then resume Buparlisib at one lower dose level. Note: Anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.
Grade 4 (≥ 10 stools/day > pretx)	If diarrhea can be controlled with optimal anti-diarrheal treatment, continue Buparlisib. If not, for diarrhea ≥ grade 3, interrupt treatment until resolved to ≤ grade 1, then resume Buparlisib at one lower dose level. Note: Anti-diarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea.
Cardiac	
Cardiac – Left Ventricular Systolic Dysfunction	
Asymptomatic, resting ejection fraction 40 – 50%; or 10-20% drop from baseline	Maintain dose level and repeat LVEF measurement at 2 month intervals until return to baseline
Symptomatic, responsive to intervention,	Omit dose until resolved to ≤ Grade 1, then ↓ by 1 dose level LVEF measurement to be repeated; if not resolved to ≤ Grade 1

ejection fraction 20 – 39% or > 20% drop from baseline	within 3 weeks, permanently discontinue Buparlisib
Refractory or poorly controlled, ejection fraction < 20%	Omit dose and discontinue Buparlisib
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) and/or > 60 ms change from baseline on ECG, first occurrence	• Omit Buparlisib • 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, Buparlisib may be restarted at a one lower dose level • Discontinue Buparlisib • 24 hour Holter monitoring for all patients
QTcF> 500 ms (≥ Grade 3) and/or >60 ms change from baseline on ECG, two separate occurrences	
Other Cardiac Events	
Grades 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ by 1 dose level
Grade 4	Omit dose and discontinue Buparlisib
General Adverse Events	
Rash	
Grade 1	Maintain dose level. Consider initiation of 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 ≤ 14 days, ↓ 1 dose level • If resolved in > 14 days (despite appropriate skin toxicity therapy), discontinue Buparlisib
Grade 4	Omit dose and discontinue Buparlisib
Photosensitivity	
Grade 2 (painful erythema)	Interrupt Buparlisib until resolution to ≤ grade 1, then : • If resolution to grade ≤ 1 in ≤ 14 days, resume Buparlisib decreased by one dose level; • If resolution to ≤ grade 1 takes > 14 days, discontinue Buparlisib
Grade 3 (erythema with desquamation)	Discontinue Buparlisib
Grade 4 (life threatening; disabling)	Discontinue Buparlisib
Fatigue	
Grade 3	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ by 1 dose level
Grade 4	Omit dose and discontinue Buparlisib
Any CTCAE Grade 3 Non-Hematological Toxicity not listed above	Interrupt treatment until resolution to ≤ grade 1, then resume Buparlisib at one lower dose level
Any CTCAE Grade 4 Non-Hematological Toxicity not listed above	Discontinue Buparlisib
Other Non-Hematologic Toxicities	

Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ by 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 antiemetics
Hematological Toxicities	
Neutropenia	
Grade 1 (ANC < LLN – 1.5 x 10^9/L) Grade 2 (ANC < 1.5 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 ↓ by 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ by 1 dose level
Thrombocytopenia	Omit dose until resolved, then ↓ by 1 dose level
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 ↓ by 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ by 1 dose level
Treatment Delay ≥ 3 weeks	
Any hematologic or non-hematologic toxicity requiring interruption for ≥ 3 weeks	Discontinue Buparlisib

9.4 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication. All patients will be provided with a pill diary to record daily drug self-administration.

9.5 Concomitant therapy

All medications (excluding prior chemotherapy and biologic, immunologic or radiation therapy) taken within 4 weeks prior to the administration of Buparlisib 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 Buparlisib should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions described in section 9.5.1.

9.5.1 Drugs that are prohibited

- Other investigational therapies must not be used while the patient is on the study.
- Anticancer therapy (chemotherapy, biologic, or radiation therapy) other than the study treatment must not be administered to patients while they are 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 Buparlisib is predominantly mediated by CYP3A4 (fm>0.9), with only minor contributions of CYP1A1. As Buparlisib is a sensitive CYP3A4 substrate, co-administration of Buparlisib with strong and moderate CYP3A4 inhibitors and CYP3A4 inducers (which are predicted to reduce systemic exposure to Buparlisib and thereby increasing the risk of exposing patients to subtherapeutic drug levels) is prohibited.
- Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants are not permitted.
- 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), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
- Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective in this study.
- If a patient requires the concomitant use of any medication included in Table 5.4 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.

9.5.2 Drugs to be used with caution

Preliminary in vitro metabolism studies suggest that Buparlisib is a weak, reversible inhibitor of 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 of CYP2C8/2C9/2C19 (IC_{50}=34 μM, [I]/IC_{50}=0.15). Note that with the data available, we are unable 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. See Appendix A for a full list of drugs that are prohibited and drugs that must be used with caution. Caution is particularly advised when Buparlisib 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 guidelines. It is recommended that treatment start with metformin.
- Concomitant treatment with corticosteroids and Buparlisib should be avoided, whenever possible, during this study. A short duration (< 2 weeks) of systemic corticosteroids is allowed

(e.g. for chronic obstructive pulmonary disease, or as an anti-emetic). Chronic dosing of corticosteroids is known to induce CYP3A enzymes, thereby increasing the risk of reducing Buparlisib overall exposure to sub-therapeutic levels.

- If a patient, after study enrollment, requires the concomitant use of any medication which may cause QT prolongation and/or Torsades de Pointes (Table 5.3), then the investigators, at their discretion, may co-administer such medications. Patients receiving such medications must be monitored.
- Unless otherwise indicated, investigators should use their clinical discretion if any other concomitant medications known to be metabolized by CYP2C8, CYP2C9, CYP2C19 and/or CYP3A4/5 need to be co-administered with Buparlisib. Patients should be carefully monitored for signs of possible toxicity due to any individual concomitant medications.
- Please refer to a list of known medications that are substrates, inhibitors, and inducers (provided in Appendix A) of CYP2C8, CYP2C9, CYP2C19 and/or CYP3A4/5 isoenzymes as well as QT prolonging drugs and carefully consider their co-administration with Buparlisib.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 3 Evaluation and Visit Schedule

Procedure		Screening	Cycle 1		Cycle 2		Additional Cycles (Cycle ~28 days)	Post-treatment/ Withdrawal	Survival/ Follow-up
	<30 days prior to tx start	≤14 days prior to tx start	Day 1 (±2 days)	Day 15 (±2 days)	Day 1[1] (±2 days)	Day 15 (±2 days)	Day 1[1] (±2 days)	(4 weeks after last treatment) +/-7 days[19]	
Informed Consent	X								
Medical History		X							
Serum Pregnancy Test (WOCBP)[2]		X Within 48 hrs	As clinically indicated						
Vital Signs[18]		X	X	X	X	X	X	X	
Physical Examination		X	X	X	X	X	X	X	
Karnofsky Performance Status		X	X		X		X		
Adverse Events[3]			X	X	X	X	X		
Concomitant Medications		X	X	X	X	X	X	X	
Neuro-psychiatric questionnaire[4]		X	X	X	X	X	X	X	
Patient Pill Diary[5]			X		X		X		
Hematology[6]		X	X	X	X	X	X	X	
Serum Chemistry (Fasting)[7]		X	X	X	X	X	X	X	
Screening Bloods[8]		X							
Coagulation Profile[9]		X	X		X		**Even Cycles**[9]	X[9]	
Urinalysis[10]		X						X	
12-lead ECG[11]	X		X		X		X	X	
ECHO/MUGA[17]	X						X		
Chest X-ray[12]	X		Every 8 weeks from start of treatment						
Radiological tumor response assessment[13]	X		Every 8 weeks from start of treatment						
Buparlisib[14]			X[14]→	→	→	→	→		
Survival Status[15]									X
Tumor tissue Evaluation[16]	X								

1. Cycle = 28 days, Day 28=Day 1of next cycle.

2. Serum pregnancy test must be performed for all women of childbearing potential <u>within 48 hours</u> of starting study drug. Additional testing will be performed as clinically indicated.

3. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.

4. PHQ-9 and GAD-7 questionnaires will be completed at Screening, C1D1, C1D15, C2D1, C2D15 and on Day 1 of subsequent cycles. The questionnaires should also be completed at the end of study treatment visit. Symptomatic patients may require more frequent questionnaires – please see Section 11.2 for more information.

5. At the start of each cycle, patients will be given a Pill Diary and asked to record the time, date, and side-effects of each dose of Buparlisib taken. Patient diaries are collected at the end of each cycle.

6. 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. This should be performed on D1 and D15 of cycle 1 and cycle 2 and day 1 of all subsequent cycles.

7. Serum Chemistry: Patients must be fasting overnight for at least 8 hours prior to blood sampling. These tests should be performed on D1 and D15 of cycle 1 and cycle 2, and day 1 of all subsequent cycles. C1D1 assessments may be performed up to 72 hours prior to the scheduled visit. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested as well upon receipt of the chemistry panel results.
Serum Chemistry includes:

- **Comp with conjugated bilirubin (*urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, glucose, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase (fractionated if alkaline phosphatase level is grade 2 or higher), AST (SGOT), ALT (SGPT))***
- **Lipid Panel *(total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides)***
- **Lactic dehydrogenase (LDH)**
- **Phosphorus**
- **Uric acid**

8. Screening tests should be performed ≤14 days prior to treatment start. These tests include:

- **Magnesium**
- **Amylase, lipase, and GGT**

9. Coagulation - PT or INR and PTT C1D1 assessments may be performed up to 72 hours prior to the scheduled visit. Additional assessments will be performed on Day 1 of Cycle 2 and repeated every even cycle (≤ 72 hours prior to the scheduled visit). A repeat coagulation profile panel is required at the time of study treatment discontinuation. Patients entering the study while receiving anticoagulation therapy or those who are initiated on anticoagulation therapy while on study should have their coagulation profile performed at every visit.

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

11. A standard 12 lead ECG is to be performed at screening and significant findings must be recorded. ECGs will be performed at the beginning of each cycle. However, the C1D1 ECG is not required if the baseline ECG was performed within 7 days.

12. A Chest X-Ray should be performed for all patients at screening and every 8 weeks from start of treatment until progression as per RECIST. Chest CT is an acceptable alternative to a screening chest x-ray.

13. Screening radiological assessments should be performed within 4 weeks of the first dose. Radiological assessments include baseline abdominal and pelvic CT scan and/or MRI of the abdomen and pelvis. In patients with osseous lesions, bone X-rays and/or bone scans should be obtained. Radiological tumor assessment should be performed at baseline within 30 days before start of treatment and subsequently every 8 weeks (2 cycles), until progression of disease or end of treatment. All radiological assessments should be performed within ±7 days of the scheduled day of assessment.

14. Buparlisib: Buparlisib will be orally self-administered, once daily in the morning, at a dose of 100 mg (two 50 mg capsules). Patients will receive a prescription for a 4-week supply of drug at the beginning of each cycle. The Buparlisib drug bottles (including any unused capsules) will be returned to the clinic for drug accountability at the end of each cycle.
X^{14}→: Start and continue treatment. → : Continue treatment.

15. Post-study survival status: Follow-up survival information will be collected for all patients by clinic visit or telephone contact approximately every 6 months from the date of first dose of Buparlisib. Patients will be followed until disease progression and/or death.

16. For all patients enrolling to the Phase II portion, pre-treatment tumor tissue specimens will be analyzed using immunohistochemistry for PTEN expression levels. *M*utation testing may also be performed on samples.

- **Pretreatment tumor tissue specimens will be analyzed to detect markers of activation of the PI3K-Akt pathway as well as additional alterations that may impact upon sensitivity to Buparlisib. Levels of PTEN expression will be measured utilizing immunohistochemistry. All tumors will be classified based upon level of PTEN expression. If normal DNA is required, patients may be asked to provide peripheral blood or a saliva sample during study participation for comparison with the tumor tissue. DNA extracted from samples may be sequenced to detect multiple alterations in both the PI3K/Akt pathway in additional genes that may condition response to Buparlisib. Other sequencing methods may also be used to screen tumor and germline DNA for commonly occurring mutations in genes within the PI3K-Akt pathway, including *AKT*, *PIK3CA*, and *FGFR3*. Extracted DNA will be sequenced to detect potential mechanisms of resistance to Buparlisib.**

  Patients enrolling in the Expansion Cohort must have prior mutational testing demonstrating alterations predicted to activate the PI3K/Akt/mTOR pathway..

17. A screening echocardiogram (ECHO) or multigated acquisition scan (MUGA) will be performed and repeated every 3 cycle unless a drop in EF occurs as described in Table 2.

18. Vitals include: heart rate, blood pressure, respiration rate, temperature, weight and height. Height is only required at baseline.

19. The post-treatment/withdrawal visit can be foregone for patients who are too unwell to attend or for other reasons at the investigators discretion. Patients may be contacted by phone to assess resolution of toxicities, and may be contacted for survival follow up.

11.0 TOXICITIES/SIDE EFFECTS

Risks are possible side effects of study medication or another medicine, and those related to any of the study procedures (e.g. taking blood, biopsy, imaging, etc).

Based on information from patients already treated with Buparlisib alone or in combination with other medicines, the most frequently reported side effects (in more than 20% of patients) include, but may not be limited to: decreased appetite, nausea, vomiting, diarrhea, abdominal pain, constipation, feeling weak or tired, rash with or without itching, inflammation and pain in the mouth and other mucosal areas, mood disorders (such as depression, anxiety or irritability), shortness of breath, cough, and changes in blood tests such as increase in blood sugar, alteration in liver tests, decrease in red blood cell counts, changes in white blood cells counts, longer time for blood clotting and change in levels of some electrolytes (e.g. potassium, sodium).

Less frequent side effects (in more than 5% of patients) include: indigestion and disturbance of taste, weight loss, fever, headache, dizziness, confusion, change in blood pressure, pain in joints and extremities, swelling, sleep disturbances, urinary tract infection, changes in blood tests for kidney and pancreas function.

Uncommon events (less than 5% of patients) that may nevertheless be medically important include: skin infection, allergic reactions, eye effects (such as blurred vision, conjunctivitis), lung infection/ inflammation. A few cases reported visual hallucinations, seizures and alterations in nerve functioning (mainly in combination with paclitaxel). One case was reported in a patient with advanced lung cancer committing suicide.

Rare cases of encephalopathy have been described, including PRES (posterior reversible encephalopathy syndrome).
BuparlisibBuparlisibBuparlisib

11.1 Toxicity Monitoring

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 CTCAE v4.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf

11.2 Neuropsychiatric events

In [CBuparlisibX2101], 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 Buparlisib. Three 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 and/or anxiety also developed mood alterations when treated with Buparlisib at the 100 mg dose level, 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 a history of or active 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 (2nd generation antipsychotics such as olanzapine and quetiapine) and antidepressants may be applied as per the investigator's discretion and following consultation with a psychiatrist. Buparlisib dose will be omitted for any patient with mood alterations requiring mood stabilizers until their mood alteration has resolved to ≤ Grade 1. A log will be maintained of all patients who are discontinued from this trial based on questionnaire responses during study.

11.2.1 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

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

- Screening
- Days 1 and 15 of Cycle 1
- Days 1 and 15 of Cycle 2
- Day 1 of Cycle 3 and subsequent cycles (only for patients who have not shown mood alterations during the first cycle; patients who did should continue to fill out the questionnaire on an every other week basis).
- End of Study treatment
- Additional assessments may be done according to the clinical judgment of the Investigator.
- 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).

The PHQ-9 and GAD-7 in the protocol appendix or in the MSKCC Medical Records Forms may be used. All questionnaires will be reviewed by a research staff member. The following grading system will be used for this study:

Table 4 Toxicity grading based on mood questionnaire scores

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

At screening, a patient as judged by the investigator or who meets the cut-off score of ≥ 10 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, 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 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). Please see Table 2 for further details on changes in drug dosing in response to symptoms. If an investigator feels that a patient requires a dose reduction and/or dose delay other than those specified herein, this may be allowed after communication with the Principle Investigator, and would not be considered a protocol violation.

11.3 Hyperglycemia

In preclinical studies, insulin/glucose homeostasis was impacted in various species (mice, rats, dogs), as expected from the mode of action of Buparlisib. 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 Buparlisib in patients with solid tumors (CBuparlisibX2101). 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 Buparlisib treatment investigators are advised to adhere to the protocol guidelines outlined in table2.

11.4 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. ECG abnormalities and QT prolongation have been noted in CBuparlisibX2101 as detailed in section 3.4.2. As a precaution, 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 Buparlisib 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.

11.4.1 Management of Cardiac events

At screening, a 12-lead electrocardiogram (ECG) and an ECHO/MUGA will be performed at the Screening Visit to assess eligibility and at the end of treatment. Repeat ECGs will be performed at the

beginning of every cycle and ECHO/MUGA after every third cycle. Please refer to Table 2 for the management of specific cardiac toxicities and drug dose adjustments.

11.5 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 Buparlisib in the single agent setting two cases of Pneumonitis occurred. In the study BuparlisibX2101 one patient experienced Pneumonitis grade 2 eight weeks after the first dose of Buparlisib at 100mg which resolved in 7 days after antibiotic therapy and discontinuation of the study treatment due to fatigue. In the Japanese study BuparlisibX1101 one case of Pneumonitis occurred in a patient given 100 mg one month after the start of study medication with Buparlisib. 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 Investigator's Brochure for more details).

All patients participating in clinical trials administering Buparlisib 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 2 should be followed. Consultation with a pulmonologist is highly recommended for any pneumonitis case identified during the study.

11.6 Management of Liver Toxicities

Monitoring of liver function tests will be performed at:

- Screening
- Days 1 and 15 of cycles 1 and 2
- More frequently if clinically indicated and in patients with borderline acceptable AST, ALT, and/or bilirubin values at screening

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

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

Patients who discontinued study treatment should be monitored weekly or more frequently if

clinically indicated **until resolved to ≤ grade 1 or stabilization** (no CTCAE grade change over 4 weeks).

11.7 Reproductive Risks

Male and, to a lesser extent, female reproductive organs were found to be targets of toxicity of Buparlisib in both rats and dogs. 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 are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 12 weeks after stopping treatment. Highly effective contraception is defined as either:
    - 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.
    - 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.
    - Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of a combination of any two of the following:
        - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - Oral contraception as well as injected or implanted hormonal methods are not allowed as Buparlisib potentially decreases the effectiveness of hormonal contraceptives.
    - Fertile males, defined as all males physiologically capable of conceiving offspring must use condoms during treatment and for an additional 12 weeks after study drug discontinuation and should not father a child during this period.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression will be evaluated in this study using the international criteria by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI*, 92(3):205-216, 2000; EJC, 45(2):228-247, 2009]. Changes in the largest diameter (uni-dimensional measurement) are used in the RECIST v1.1 criteria. Note: lesions are either measurable or non-measurable using the criteria provided below:

12.1 Definitions

Measurable lesions: lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm by clinical exam or with spiral CT scan (irrespective of scanner type) or MRI (no less than double the slice thickness and a minimum of 10mm). Malignant lymph nodes must be 15 mm in the short axis when assessed by spiral CT scan to be considered measurable. Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability previously described. Blastic bone lesions are unmeasurable. Tumors that are situated in a previously irradiated area are measurable only if unequivocal growth can be documented.

Non-measurable lesions: all other lesions (or sites of disease) including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly (not followed by CT or MRI) are all non-measurable.

Target lesions: all measurable lesions – up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs – should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions: all other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

12.3 Response Criteria

12.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute

	increase of at least 5 mm.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

12.3.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

12.3.4 Confirmation of Response

There will be no repeat imaging studies done solely for the purpose of confirming response. Patients

will have follow-up imaging studies as outlined in the protocol and responses that are confirmed on follow-up scans will be noted.

12.3.5 Duration of Overall Response/Progression Free Survival

The duration of overall response is measured from the time that measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Progression Free Survival will be calculated from the start of treatment until progressive disease or death. Patients who die before documented progression will be considered failures at their time of death. If the patient did not progress or die, the patient will be censored on the date of last follow-up.

13.1 CRITERIA FOR REMOVAL FROM STUDY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Dose delay of > 21 days from the previous dose
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Inability of subject to comply with study requirements

If at any time the patient is found to be ineligible for the protocol as designated in the inclusion and exclusion criteria detailed in Section 6.0 (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

The purpose of this study is to assess the efficacy of Buparlisib in patients with progressive urothelial cancer who have received prior cytotoxic chemotherapy. Historically, patients in this setting experience a median PFS of 2-3 months (Vaughn 2002; Dreicer 2007; Gallagher 2008). Thus, the primary endpoint of this study will be the proportion of patients who are progression-free after eight weeks on-study. Kaplan-Meier analysis of PFS will be performed.

Patients will not be considered evaluable for the primary objective (PFS rate at 8 weeks) if they receive < one cycle of protocol therapy and are discontinued from protocol treatment for either rapid clinical deterioration related to progression of disease, withdrawal of consent, or adverse events unrelated to Buparlisib. These patients will be replaced. They will still be evaluable for toxicity assessment.

To establish the safety and toxicity of Buparlisib, the frequency of toxicity will be tabulated according to the NCI Common Toxicity Criteria, version 4.0.

For the Phase II portion of the study:

A minimax Simon two stage study design will be utilized with a PFS rate at 8 weeks of <60% considered not promising while a PFS rate of 80% or greater is considered promising. In stage I of the trial, 13 evaluable patients will be accrued to the study. If 8 or more patients demonstrate either progression on imaging or death after two months on-study, the study will be terminated early and declared to have a negative result. If 9 or more are progression-free at two months, enrollment will be extended to accrue a total of 35 patients. If 26 or more are progression-free after their two month scan (i.e., after stage 2), the treatment will be considered effective and worthy of further testing.

For the purposes of this study, the Type I (false acceptance of a non-promising therapy) and Type II (false rejection of a promising therapy) error rates have been set at 0.05 and 0.20, respectively. This statistical design would effectively discriminate between two-month PFS rates of <60% and >80% and yields 80% probability of a positive result if the true two-month PFS rate is >80%. It yields 95% probability of a negative result if the true two-month PFS rate is <60%. The probability of early stopping under the null hypothesis is 65%.

The secondary endpoint of response rate will be estimated as the proportion of patients meeting the criteria outlined above for a complete response or partial response. This proportion will be reported along with its binomial confidence interval.

An accrual rate of 2-4 patients per month is anticipated with an expected accrual time of approximately 10-20 months for this study.

Buparlisib
Another secondary end-point involves correlating outcome with an activated PI3 kinase pathway. Patient samples will be sequenced for mutations in PTEN and PIK3CA as well as for reduced or absent PTEN expression. Patients will be categorized on the basis of PTEN expression levels into three categories: no expression, low expression, or high expression. PTEN levels and PTEN and PIK3CA mutation status (present/absent) will be correlated with PFS using a log rank test, and with response to treatment (complete response/partial response versus no response) using Fisher's exact test.

For the Expansion Cohort:

A one-arm study design will be utilized with a PFS rate at 8 weeks of < 60% considered not promising while a PFS rate of 85% or greater is considered promising. 21 evaluable patients whose tumors harbor genetic alterations predicted to upregulate the PI3K/Akt/mTOR pathway will be accrued to this cohort. If 16 or more patients are progression-free at two months, the treatment will be considered effective and worthy of further testing.

The secondary endpoint of response rate will be estimated as the proportion of patients meeting the criteria outlined above for a complete response or partial response. This proportion will be reported along with its binomial confidence interval.

An accrual rate of 1-2 patients per month is anticipated with an expected accrual time of approximately 10-20 months for this study.

For the purposes of this cohort, the Type I (false acceptance of a non-promising therapy) error rate has been set at .10 and the power (acceptance of a promising therapy) is approximately .92.

15.1 RESEARCH PARTICIPANT REGISTRATION

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

Not applicable.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. The data collected for this study will be entered into the Clinical Research Database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org /irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees, *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

17.1.1 Risks of treatment and provisions for preventing adverse events

Potential risks to human subjects include drug related toxicity, pain and discomfort associated with Buparlisib side effects, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan). The side effects and potential toxicities of Buparlisib are listed in section 11. All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests. If an adverse medical event occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information recorded.
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.

17.1.2 Alternatives/Options for treatment

Patients can elect to receive conventional chemotherapeutics such as paclitaxel or pemetrexed for their metastatic urothelial cancer. However, there is no FDA-approved drug in this setting. Patients can also elect to receive best supportive care or to participate in another clinical trial. Participation in a clinical trial is voluntary.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. The report will be forwarded to the FDA by the Institutional SAE staff through the IND Office.

17.2.1 Serious Adverse Event (SAE) Reporting to Novartis

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

All events must be reported, by FAX (877-778-9739), to Novartis Pharmaceuticals DS&E

Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

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

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

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

- After the patient is enrolled and until 4 weeks after the patient has stopped study treatment/participation
- After the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment
- After protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks after the patient has stopped study treatment

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

The investigator must assess and record the relationship of each SAE to Buparlisib, complete the MSKCC CRDB SAE Report and send the completed, signed form by fax (888-299-4565) within 24 hours to the Novartis Drug Safety and Epidemiology Department.

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

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

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

Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

17.2.1.1 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 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.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive

a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A

Table 5.1 List of prohibited CYP3A inhibitors (strong and moderate) and CYP3A inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	aprepitant	avasimibe	Bosentan
conivaptan	atazanavir	Phenobarbital (barbiturates)	Efavirenz
grapefruit juice	cimetidine	carbamazepine	Etravirine
indinavir	ciprofloxacin	phenytoin	Modafenil
itraconazole	darunavir	rifabutin	Nafcillin
ketoconazole	diltiazem	rifampin	Ritonavir
lopinavir	erythromycin	St. John's wort	Talviraline
mibefradil	fluconazole		Tipranavir
nefazodone	tofisopam		
nelfinavir	verapamil		
posaconazole	amprenavir		
ritonavir	fosamprenavir		
saquinavir	elvitegravir		
telithromycin	tipranavir		
troleandomycin			
voriconazole			

This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase Buparlisib AUC > 5-fold, and moderate inhibitors are predicted to increase Buparlisib 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 5.2 List of CYP450 substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	adinazolam	Felodipine[1]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	fentanyl[2]
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	flunitrazepam
repaglinide	fluvastatin	clomipramine	alprazolam	fluticasone[1]
Rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	lovastatin[1]
Torsemide	gliclazide	diazepam	aripiprazole	maraviroc[1]
Troglitazone	glimepiride	fluoxetine	atorvastatin	midazolam[1]

glipizide	imipramine	Brecanavir	nifedipine
indomethacin	lansoprazole	brotizolam[1]	nisoldipine
irbesartan	mephobarbital	budesonide[1]	nitrendipine
ketobemidone	moclobemide	buspirone[1]	perospirone[1]
lornoxicam	omeprazole	Capravirine	quinine
losartan	pantoprazole	cerivastatin	sildenafil[1]
meloxicam	progesterone	chlorpheniramine	simvastatin[1]
naproxen	quazepam	cyclosporine[2]	sirolimus[1,2]
nateglinide	rabeprazole	darifenacin[1]	Tolvaptan
piroxicam	sertraline	diazepam	trazodone
Rosiglitazone	S-mephenytoin	diergotamine[2]	triazolam[1]
S-ibuprofen		ebastine[1]	
sulfamethoxazole		eletriptan[1]	
tenoxicam		eplerenone[1]	
tolbutamide		ergotamine[2]	
torsemide		estazolam	
valdecoxib		everolimus[1]	

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

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

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

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

Table 5.3 List of QT prolonging drugs to be used with caution

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

Drug	QT risk	Comment
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	
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	

Drug	QT risk	Comment
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Table 5.4 Prohibited QT prolonging drugs with risk of Torsades de Pointes

Drug	QT risk(*)	Comment
Amiodarone	known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	known risk for TdP	
Astemizole	known risk for TdP	No longer available in US. CYP3A4 substrate with narrow therapeutic index.
Bepridil	known risk for TdP	Females>Males
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Cisapride	known risk for TdP	Restricted availability; Females>Males.
Disopyramide	known risk for TdP	Females>Males
Dofetilide	known risk for TdP	
Domperidone	known risk for TdP	Not available in the US.
Droperidol	known risk for TdP	
Halofantrine	known risk for TdP	Females>Males
Haloperidol	known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	Females>Males
Levomethadyl	known risk for TdP	Sensitive CYP3A substrate
Mesoridazine	known risk for TdP	
Methadone	known risk for TdP	Females>Males
Pentamidine	known risk for TdP	Females>Males
Pimozide	known risk for TdP	Females>Males. Sensitive CYP3A substrate with narrow therapeutic index
Probucol	known risk for TdP	No longer available in U.S.
Procainamide	known risk for TdP	
Quetiapine	possible risk for TdP	Prohibited as drug is a sensitive CYP3A substrate
Quinidine	known risk for TdP	Females>Males. Sensitive CYP3A substrate
Sotalol	known risk for TdP	Females>Males
Sparfloxacin	known risk for TdP	
Tacrolimus	possible risk for TdP	Prohibited as drug is a sensitive CYP3A substrate with narrow therapeutic index
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	possible risk for TdP	Prohibited as drug is a sensitive CYP3A substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.		

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