A Phase II Trial Of Buparlisib (BKM120) In Patients With Recurrent/Refractory Primary Central Nervous System Lymphoma (PCNSL) and Recurrent/Refractory Secondary Central Nervous System Lymphoma (SCNSL)

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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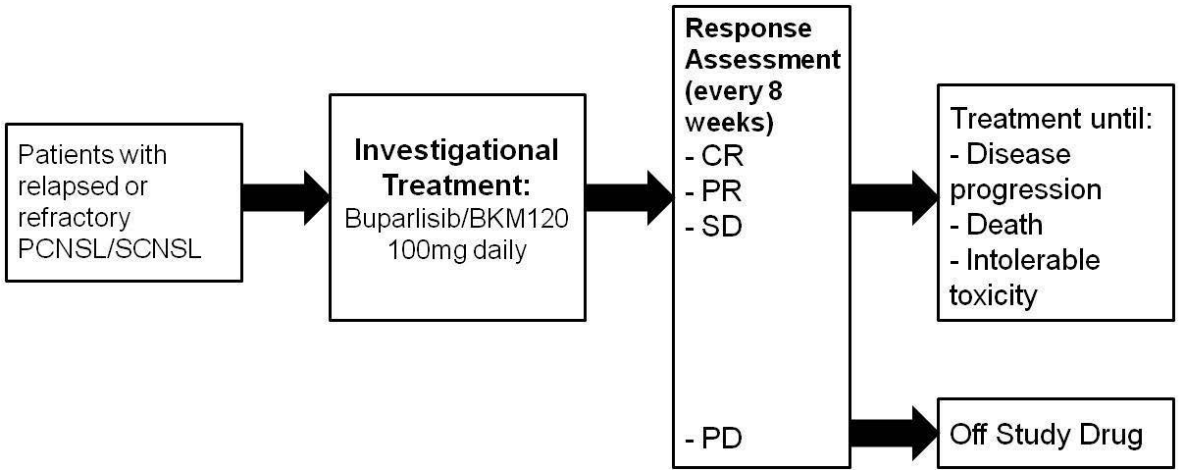
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an open-label, phase II trial of the pan-PI3K inhibitor buparlisib (BKM120) for patients with recurrent or refractory primary central nervous lymphoma (PCNSL) and recurrent or refractory secondary central nervous lymphoma (SCNSL). Patient will be treated with single agent, daily dosed buparlisib and followed to assess efficacy and toxicity.

Figure 1: Study Design Overview



CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective:

- To explore the therapeutic efficacy of buparlisib in patients with PCNSL and SCNSL as measured as progression free survival at 24 weeks (PFS24w)

2.2 Secondary Objectives:

- To explore the safety and tolerability of buparlisib in PCNSL and SCNSL patients by assessing the frequency and severity of adverse events
- To assess overall response rate (ORR) on MR imaging in patients with PCNSL and SCNSL receiving buparlisib
- To assess progression free survival at 12 weeks (PFS12w) and 48 weeks (PFS48w) in patients with PCNSL and SCNSL receiving buparlisib
- To assess the duration of response (DoR) and overall survival (OS) in patients with PCNSL and SCNSL receiving buparlisib
- To evaluate CSF pharmacokinetics of buparlisib by measuring drug concentration in serum and CSF samples

2.3 Exploratory Objectives:

- To correlate differences in drug response to PI3K pathway activation status through mutational and immunohistochemical analysis of PI3K pathway members such as but not limited to phospho-AKT, phospho-S6, phospho-4EBP1
- To characterize mutational abnormalities in paired tumor/germline DNA in PCNSL/SCNSL patients and correlated with drug response

- To correlated changes on ADC/DWI/perfusion MRI imaging to drug response
- To assess neurologic functioning using the Neurologic Assessment in Neuro-Oncology (NANO)

3.0 BACKGROUND AND RATIONALE

3.1 Primary central nervous system lymphoma (PCNSL)

PCNSL is an aggressive subtype of diffuse large B-cell lymphoma (DLBCL) with increasing incidence over the last decade (Deangelis, 2006). PCNSL usually develops in the brain but can also involve other compartments of the CNS including spinal cord, meninges, cerebrospinal fluid, and eyes. Compared to systemic DLBCL, PCNSL has a poorer prognosis (Ferreri 2011) with a cure rate of around 20-30% (Reni, Ferreri et al. 1997; Gavrilovic, Hormigo et al. 2006). Prognosis is especially poor for patients over age of 60 and patients with relapsed/refractory disease. The management of this disease poses a difficult challenge in neuro-oncology. Median survival for patients with progressive disease without treatment is two months. Unfortunately, the optimal salvage regimen is not known and only a few prospective clinical trials have addressed this patient population. In contrast to other CNS malignancies, patients with PCNSL are mainly treated with conventional methotrexate-based chemotherapy and targeted agents have not been introduced into the treatment regimen of PCNSL. Even in patients with treatment resistant PCNSL, further chemotherapy or radiation is used. Targeting molecular abnormalities has not been advanced in PCNSL mainly because the molecular pathogenesis of PCNSL remains still largely unknown due to the relative rarity of this disease and the fact that tumor tissue is usually collected in only small quantities for diagnostic purposes. In systemic lymphoma, gene expressions profiling has identified two major subgroups: germinal center type and activated B cell (ABC) the latter being associated with a poorer clinical prognosis (Alizadeh et al., 2000) but ABC DLBCL cell lines have shown to respond remarably well to targeted inhibition of the phosphatidylinositol-3-kinase (PI3K) pathway (Kloo, 2010). More than 95% of PCNSL cases are of the ABC/non-germinal center subtype (Camilleri-Broet, Criniere 2006). Therefore, the use of PI3K inhibitors could be promising in PCNSL, particularly in patients that have failed conventional methotrexate-containing chemotherapy regimens.

3.2 Secondary CNS Lymphoma (SCNSL)

SCNLS represents CNS involvement through direct invasion by a systemic non-Hodgkin lymphoma. SCNSL incidence has increased with more effective first-line therapy of systemic DLBCL. SCNSL most commonly presents with concurrent systemic progression of lymphoma and carries a poor prognosis with a median survival of 1-5 months (Grier and Batchelor, 2005). Involvement of the CNS may include the brain and leptomeninges. Like PCNSL, SCNSL therapy is challenging and usually involves methotrexate-based chemotherapy. For patients failing chemotherapy, palliative radiation can be offered but prognosis is dismal.

3.3 Relapsed/refractory PCNSL

Patients who relapse after initial therapy have an especially poor prognosis (Tyson, Siegal et al. 2003; Ferreri 2011) with a rapidly downhill and aggressive clinical course (Ferreri 2011). Based on long-term follow-up data, the relapse rate after high-dose methotrexate-based therapy with or without consolidation whole-brain radiation is 44% (Gavrilovic, Hormigo et al. 2006). The site of relapse is frequently in the brain but can also be in other compartments of the CNS or more than one compartment (Gavrilovic, Hormigo et al. 2006).

3.4 Current management of relapsed/refractory PCNSL

Chemotherapy treatments for relapsed/refractory CNS lymphoma are not efficacious and are associated with short progression-free survival (Table 1). Whole brain radiation therapy is used if radiation to the CNS has not been given previously but is associated with increased risk of

neurotoxicity (Ferreri 2011). HDC/ASCT has also been studied in this setting (Table 2). Clearly, new agents are urgently needed for relapsed/refractory CNS lymphoma.

3.5 The Phosphatidylinositol-3-kinase (PI3K Pathway)

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

Table 1: Salvage treatment for relapsed/refractory primary CNS lymphoma (NR: not reported)

References	No.	Treatment	Prior XRT (%)	ORR (%)	3m PFS (%)	6m PFS (%)	PFS (m)	OS (m)
Arellano-Rodrigo et al. 2003	16	VP16/IFOS/AraC	100%	37	60	30	4.5	6
Plotkin et al. 2004	22	Methotrexate	58%	91	NR	NR	26	26
Enting et al. 2004	15	Temozolomide + Rituximab	13%	53	NR	NR	2.2	10.5
Fischer et al. 2006	27	Topotecan	52%	33	NR	NR	2	8.4
Reni et al. 2007	36	Temozolomide	85%	26	NR	NR	2.8	4
Raizer et al., 2012	11	Pemetrexed	18%	55	60	45	5.7	10.1
Batchelor et al. 2011	9	Rituximab	9%	36	NR	NR	3.7	NR
Nguyen et al. 2005	27	Radiation	-	74	77	62.5	9.7	10.9

Table 2: Phase II trials of high-dose chemotherapy followed by autologous stem cell transplantation for relapsed/refractory primary CNS lymphoma

References	No.	Pre-transplant induction	High-dose Chemotherapy	Outcome
Soussain et al. 2001	22	AraC + VP16	TT/Bu/Cy (TBC)	3Y OS – 64%
Soussain et al. 2008	43	AraC + VP16	TT/Bu/Cy (TBC)	2Y OS – 45%

Constitutive activation of PI3K signaling is known to be a critical step in mediating the transformation potential of oncogenes and tumor suppressors in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2

therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006). Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers.
Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but not limited to,

- Gait-of-function mutation of PI3K subunits (*PIK3CA* encoding the PI3K at the catalytic subunit p110alpha; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g. HER2, EGFR, RAS. Src-family proteins) or
- Loss of function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g. loss of PTEN expression or function) (Chow 2006, Cully 2006)

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

3.6 The PI3K/mTOR/Akt Pathway in Lymphoma

The early experience with PI3K inhibitors in systemic lymphoma is very encouraging (Fruman 2011). Systemic lymphomas, and its most common subtype diffuse large B-cell lymphoma (DLBCL) can be distinguished based on their gene expression profiling into germinal center type and activated B cell center (ABC) type (Alizadeh 2000). ABC- type DLBCLs have a poorer clinical outcome but ABC cell lines respond remarkably well to PI3K inhibition (Kloo 2010). Inhibition of the PI3Kdelta isoform seems to be particularly effective in ABC DLBCL, consistent with the prominent role of PI3Kdelta-mediated signaling in lymphocyte biology (Fruman 2011).

3.7 The PI3K/mTOR/Akt Pathway in PCNSL

Utilizing 12 patient-derived xenograft models from patients with intracranial lymphoma; 9/12 xenograft models are from patients with PCNSL, 3/12 xenograft models are from patients with SCNLS, we were able to demonstrate PI3K pathway activation. Using immunohistochemical staining and western blotting we observed increased phosphorylation of both 4EBP1 and ribosomal protein S6 (234/235) in all examined patient-derived orthotopic xenograft models (compared to normal mouse brain) (Fig. 2). These xenograft models also exhibited higher levels of AKT phosphorylation (Ser308 and Ser473) than intracranial xenografts from other cancer types (Fig. 2), suggesting that aberrant activation of the PI3K signaling pathway may occur upstream of AKT in PCNSL.

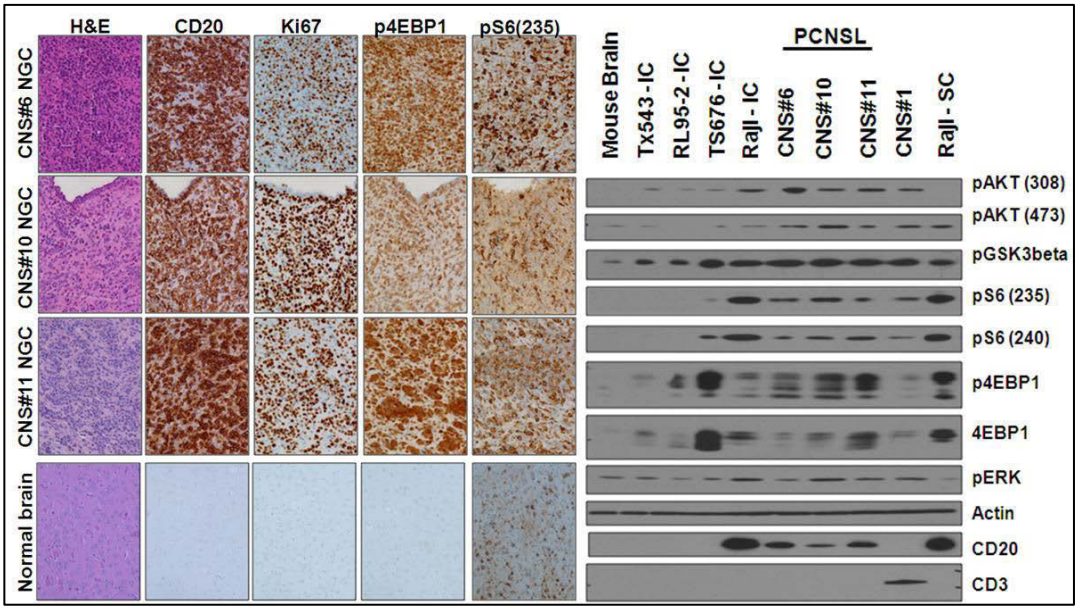


Fig. 2: PI3K-mTOR activation in PCNSL. Left panel: Increased phosphorylation of 4EBP1 and S6RP in all PCNSL xenograft models compared to normal brain (1. line: H&E, 2. line: CD20; 3. line: Ki67; 4. line: p4EBP1, 5. line: pS6RP). Right panel: Protein levels in PCNSL xenografts (line 6-9) compared to normal mouse brain (line 1) and orthotopic xenografts from other cancer types (line 2-5). TS543 and TS676: GBM; RL95-2:

endometrial CA; Raji: Burkitt Lymphoma. SC=subcutaneous; IC=intracranial.

We also established a pre-clinical ex-vivo animal model (slice cultures) to explore the effects of PI3K pathway inhibition. The pan-class I PI3K inhibitor buparlisib reduced phosphorylation levels of AKT (Ser473) dose-dependently and also induced cell death as measured by increased cleaved caspase -3 and cleaved PARP levels (Fig. 3).

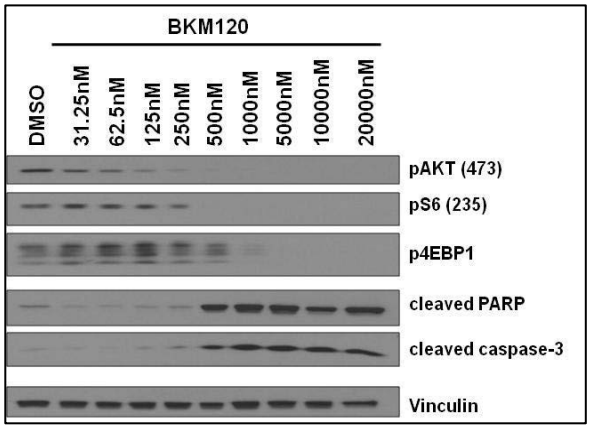
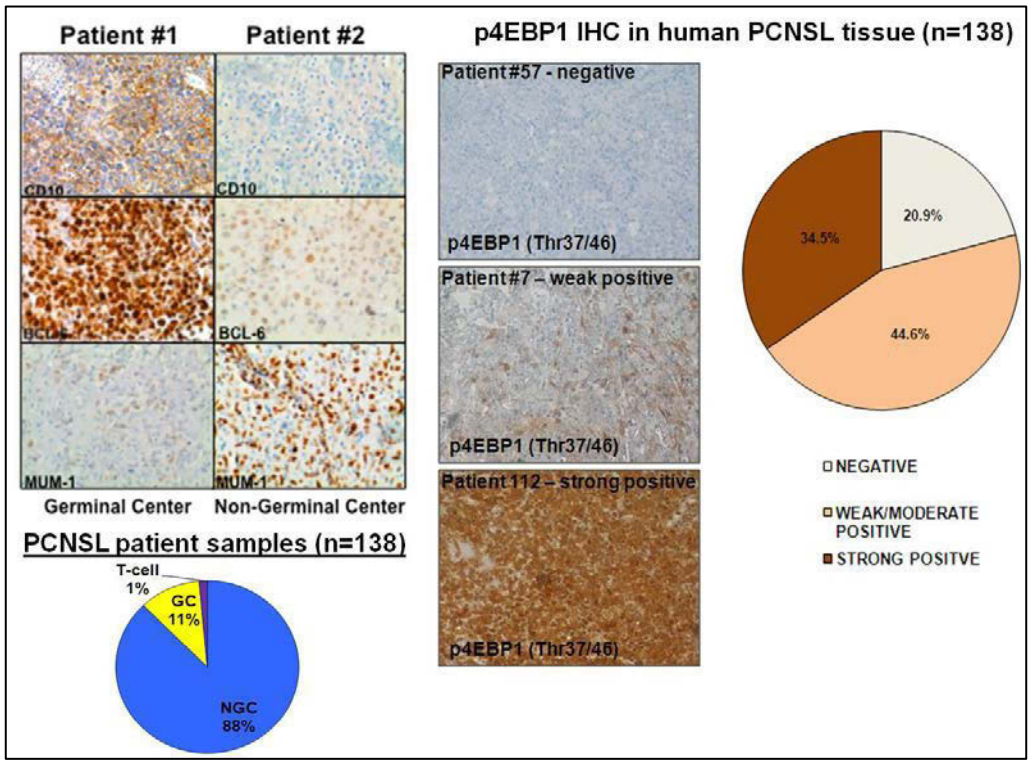


Fig. 3: *Ex vitro* Slice Culture confirm activation of PI3K pathway and inhibition through the pan-PI3K inhibitor buparlisib. Vibratome slices were treated with the pan-class I PI3K inhibitor buparlisib for 24 hours. Western blot analysis is shown for pAKT (SER473) pS6 (SER235), p4EBP1 (THR37/46), cleaved caspase-3 and cleaved PARP. Vinculin served as a loading control.

It is well known that the majority of PCNSL are of the non-germinal center or ABC subtype. We examined 138 PCNSL patient samples and observed that 88% are of the non-germinal center or ABC subtype and therefore should respond well to PI3K inhibitors. To further investigate the activation status of the PI3K pathway in PCNSL, we examined the same 138 formalin-fixed, paraffin-embedded (FFPE) human PCNSL tissue samples for PI3K pathway activation using phosphorylated 4EBP1 (phospho-site threonine 37/46) as readout. 79.1% of patient samples were positive for phospho-4EBP1 staining (Fig 4).

Fig. 4: The majority of PCNSL is of the ABC subtype and shows activation of the PI3K pathway. Left panel: IHC staining of two representative PCNSL samples for CD10 (top), BCL-6 (middle), and MUM-1 (bottom) . Overall, 88% of PCNSL in our sample set were of the non-germinal center type (according to the Hans classification). Right panel: Immunohistochemical (IHC) staining of the PI3K downstream target phospho-4EBP1 (Thr37/46). Representative images of no, weak or strong IHC signal (from top to bottom) with pie chart representing the distribution of no, weak or strong phospho-4EBP1 ICH signal in 138 PCNSL patient samples.



The PI3K/AKT/mTOR pathway has been the focus of recent advances in cancer therapeutics in the lymphoma field. Buparlisib is a potent and highly specific pan-class I PI3K inhibitor and has been extensively studied in non-clinical animal models. A maximal tolerated dose has been established and is currently being evaluated in clinical trials with oncologic indication including non-Hodgkin

lymphoma (MSK Protocol IRB # 13-072). Buparlisib is of additional interest as it has good CNS penetration and is currently being studied in a phase II trial in recurrent glioblastoma patients.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Buparlisib is a potent and highly specific oral pan-class I PI3K inhibitor and has been studied extensively in non-clinical models and is currently being evaluated in clinical trials for several oncologic indications including non-Hodgkin's lymphoma and glioblastoma.

As already stated in previous sections, inhibitors of the PI3K/Akt/mTOR pathway, including buparlisib, may be therapeutically effective in PCNSL and SCNSL patients based on the observations from pre-clinic studies with inhibitors of the PI3K pathway as well as clinical trials in non-Hodgkin lymphoma. Buparlisib, a pan-class I PI3K inhibitor with established CNS permeability, presents a particular intriguing compound to be used in the treatment of relapsed/refractory PCNSL/SCNSL.

4.1.1 Rationale for the study design

An open label, single arm, phase II study has been selected to explore the efficacy and safety of buparlisib in patients with relapsed/refractory PCNSL and relapsed/refractory SCNSL. Twenty-one patients will be enrolled of which at least 10 will have relapsed/refractory PCNSL.

No clear data exist on the effect of targeted therapy in either PCNSL or SCNSL. Additionally, no clear data exist that activation of the PI3K pathway in PCNSL or SCNSL is predictive for response to a PI3K inhibitor. Thus, enrollment of patients with activated as well as non-activated PI3K pathway is considered appropriate.

In the absence of a comparative arm but based on historical data, PFS24w is considered an appropriate primary endpoint to objectively measure anti-tumor activity.

A single arm study will be performed due to lack of approved agents as well as small patient population.

The protocol specific assessments, treatment and follow-up are consistent with a standard procedures applied in this disease setting.

4.2 Intervention

Buparlisib 100 mg once daily has been established as the maximal tolerated dose (MTD) in 2 single agent trials (CBKM120X2101 and CBKM120X1101) and one combination trial (CBKM120x2107 with trastuzumab).

Accordingly, buparlisib will be dosed at 100 mg/day (see Table 3).

Table 3: Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen
Buparlisib	Oral gelatin capsules	100 mg (2x 50mg capsules[1])	Once daily

[1] Buparlisib may be taken to consume a dose of 100 mg/day (or dose reduction level) in 50mg or 10 mg capsules, where supplied.

[2] Dose reduction levels for buparlisib will be administered according to Table 5.

For example, buparlisib 80 mg should preferentially be administered as 1x 50mg size capsule, and 3x10 mg size capsules.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Buparlisib

5.1.1 Study drug packaging and labeling

The investigational drug to be used in the course of this trial is buparlisib. Novartis Drug Supply Management or its designee will provide buparlisib as 10 mg and 50 mg hard gelatin capsules as individual patient supply, package in bottles. The capsules are packaged in HDPE bottles with a plastic child resistant closure.
The storage conditions for study drug will be described on the medication label. Buparlisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area. The investigator needs to instruct the patient to take the study drug as per the protocol.

Buparlisib will be supplied as 10-mg and 50-mg hard gelatin capsules, packaged in bottles, and will be given orally on a flat scale of mg/day (see Table 4).

Table 4: Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Buparlisib	Capsules in bottle 10 mg 50 mg	Labeled as "BUPARLISIB" Once daily dosing

5.1.2 Drug supply and storage

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access.

Upon receipt, buparlisib should be stored according to the instructions specified on the drug labels. These instructions should also be made clear to the patient for storage and self-administration of buparlisib at home.

5.1.3 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit using pills counts and information provided in the pill diary. Records of study medication used, dosages administered, and intervals between visits and the completion of the study will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

5.1.4 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a Drug Accountability Form. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed Drug Accountability Form to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.1.5 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

5.1.6 Buparlisib Administration

All participants will initiate treatment within 96 hours of registration. Buparlisib will be self-administered on a continuous once daily dosing schedule. There will be no breaks between dosing schedules.

The following general guidelines should be followed for buparlisib administration:

- Patient should be instructed to take the dose of buparlisib once daily in the morning, at approximately the same time each day.
- Buparlisib should be taken at least 1 hour following a light breakfast.
- Patient should not eat for 2 hours after the administration of each buparlisib dose.
- Buparlisib should be taken with a glass of water. Patient should swallow the capsules as a whole and not chew them.
- 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.
- If the patient forgets to take the dose before 18:00 (6PM), then the dose should be withheld that day and buparlisib should be restarted the following day.
- Patient should avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, star fruit and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment periods due to potential CYP3A interaction. Regular orange juice (Citrus X sinensis) is allowed.
- Patient must avoid concomitant intake of strong and moderate CYP3A inhibitors and induces. Detailed information on potential drug interactions and a list of prohibited concomitant CYP3A interfering medication is provided in Appendix 1.

5.1.7 Supportive care guidelines and concomitant medications

Participants must be instructed not to take any additional medications, including over-the-counter products, during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medications/therapies deemed necessary for the care of the participant are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- Strong CYP3A inhibitors and CYP3A inducers are prohibited. Moderate CYP3A inhibitor and inducers may be used with caution. In vitro studies suggest that buparlisib is a sensitive CYP3A4 substrate. Co-administration of buparlisib with strong and moderate CYP3A4 inhibitors is predicted to increase the systemic exposure to buparlisib; likewise CYP3A4 inducers can be expected to decrease systemic exposure to buparlisib, possibly resulting in sub-therapeutic drugs levels. Please refer to Appendix 1 for a list of prohibited drugs. Please note that this list may not be comprehensive.
- CYP3A and CYP2C substrates are discouraged but may be used with caution and monitoring. Particularly, caution is advised when buparlisib is co-administered with drugs that are sensitive substrate or have a narrow therapeutic index. Participants receiving such medications must be monitored for potentiation of toxicity due to any individual concomitant medications, and my require dose titration or reduction of the drug substrate. Please refer to Appendix 2 for a list of drugs. Please note that this list may not be comprehensive.
- QT interval prolonging medications known to induce Torsades de Pointes or to promote QT prolongation are prohibited (see Appendix 3). If a participant, after initiating study drug, requires the concomitant use of a drug known to prolong the QT interval, then investigators, at their discretion, may co-administer such medications with appropriate monitoring. The Primary Investigator should be consulted as soon as possible
- Concomitant use of QT prolonging medications that have a conditional or possible risk to induce Torsades de Pointes is allowed with caution and monitoring (see Appendix 4)
- Medications with the potential to alter serum electrolytes (e.g. diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias
- Herbal preparations and medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wart, Kava, ephedra (ma huang), gingko biloba, dephydroepiandosterone (DHEA), yohimbe, saw palmetto, gingseng. Participants should stop using any herbal medications 7 days prior to first dose of study drug.
- Corticosteroids should be used in the smallest possible dose to control symptoms or cerebral edema and mass effect, and discontinued if possible.
- Anti-seizure medications should be used as indicated. Only participants receiving non-enzyme-inducing anti-epileptic drugs (EIAED) are eligible. If for unavoidable clinical reasons (emergency department visit, severe allergies, toxicities, etc) a participant's AED is switched to another AED, the following guideless must be followed:
    - Participants should be started on another non-EIAED if at all possible
    - Participants who are inadvertently and temporarily changed to an EIAED should be immediately changed to an alternative non-EIAED
    - Participants who need to permanently change anticonvulsant, but who cannot change to another non-EIAED must be discussed with the Principal Investigator.
- Febrile neutropenia may be managed according to the Memorial Sloan-Kettering Cancer Center guidelines. Measures include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics will be discontinued and the participant observed.
- Routine prophylactic use of G-CSF is not permitted. However, therapeutic use in participants with serious neutropenic complications, such as sepsis, may be considered at the investigator's discretion.

- The use of antiemetics will be left to the investigators' discretion. The preferred antiemetic is metoclopramide, which is not known to prolong the QT interval.
- Since some patients with CNS lymphoma are at increased risk of developing pneumocystis jirovecii pneumonia (PJP), especially if they are on corticosteroids, prophylaxis for PJP may be considered.
- Participants who develop diabetes mellitus during the study should be treated according to the American Diabetes Association guidelines. It is recommended to start treatment with metformin in the outpatient setting and sliding scale insulin in the inpatient setting.
- Because of the potential for its interaction with study medications, warfarin sodium (Coumadin), or any other Coumadin-derived anticoagulant is not permitted at any dose. Low-molecular weight heparin is permitted. If for unavoidable clinical reasons (emergency department visit, severe allergy, toxicity, etc) a participant is started on Coumadin, they must change to a low molecular weight heparin immediately in the interest of subject safety.
- Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective birth control for this study. In addition, hormonal contraceptives may also decrease the metabolic clearance of buparlisib via CYP3A4 inhibition.
- No other anticancer therapy of any kind is permitted during the study treatment period. No other drug under investigation may be used concomitantly with the study drug.
- Therapies considered necessary for the well-being of the participant may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medication conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

The population consists of adult patients with relapsed or refractory primary central nervous system lymphoma (PCNSL) or secondary central nervous system lymphoma (SCNSL).

The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria are offered treatment in the study.

6.1 Subject Inclusion Criteria

Patients eligible for inclusion in this study have to meet all the following criteria:

- Participants must be able to understand and be willing to sign a written informed consent document.
- Subjects must be at least 18 years of age on the day of consenting to the study.
- Histologically documented PCNSL or SCNSL. Patients with SCNSL need to have cytology or tissue biopsy documenting lymphomatous involvement of the CNS
- Patients must have relapsed/refractory PCNSL or relapsed/refractory SCNSL
- All patients need to have received at least one prior CNS directed therapy. There is no restriction on the number of recurrences.
- Patients with parenchymal lesions must have unequivocal evidence of disease progression on imaging (MRI of the brain or head CT) 21 days prior to study registration. For patients with leptomeningeal disease only, CSF cytology must document lymphoma cells and/or imaging findings consistent with CSF disease 21 days prior to study registration.
- Participants must have a Karnofsky performance status (KPS) of ≥ 50.
- Participants must have adequate bone marrow and organ function shown by:

- Absolute neutrophil count (ANC) ≥ 1.5x 10^9/L
- Platelets ≥ 100 x 10^9/L and no platelet transfusion within the past 14 days prior to study registration
- Hemoglobin (Hgb) ≥ 9 g/dL and no red blood cell (RBC) transfusion within the past 14 days prior to study registration
- International Normalized Ratio (INR) ≤ 1.5
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 times the ULN.
- Serum bilirubin ≤ upper limit of normal; or total bilirubin ≤ 2.0x the ULN with direct bilirubin within the normal range in patients with well documented Gilbert Syndrome.

- Participants must be able to take oral medication.
- Patients must be able to tolerate MRI scans.
- Patients must be able to tolerate lumbar puncture and/or Ommaya taps.
- Participants must have recovered to grade 1 toxicity from prior therapy.
- Participates must be able to submit 20 unstained slides from the initial tissue diagnosis for confirmation of diagnosis and correlative studies
- Life expectancy of > 3 months (in the opinion of the investigator)

Note: Prior autologous stem cell transplant as well as radiation to the CNS is **NOT** an exclusion criterion. Prior allogenic stem cell transplant **IS** an exclusion criterion.

6.2 Subject Exclusion Criteria

Patients eligible for this study must not meet any of the following criteria:

- Patients with SCNSL actively receiving treatment for extra-CNS disease are excluded. Patient should have complete resolution of their systemic disease not requiring additional systemic therapy (e.g. maintenance rituximab or decadron).
- The patient has received prior treatment with a PI3K inhibitor, AKT inhibitor, or mTOR inhibitor (e.g. rapamycin, MK2206, perifosine, etc.).
- Patient is concurrently using other approved or investigational antineoplastic agents
- Patient has received chemotherapy or targeted anticancer therapy, monoclonal antibodies ≤ 4 weeks or 5 half-lives, whichever is shorter, or 6 weeks for nitrosourea or mitomycin-C prior to starting the study drug, or the patient has not recovered side the side effects of such therapy
- Patient who has received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered to grade 1 or better from related side effects of such therapy (except alopecia)
- Patient requires more than 8 mg of dexamethasone daily or the equivalent
- Patient is taking an enzyme inducing anti-epileptic drug (EIAED), including phenobarbital, phenytoin, fosphenytoin, primidone, carbamazepine, oxcarbazepine, eslicarbazepine, rufinamide, and felbamate. Participates must be off of any EIAED for a least two weeks prior to starting the study drug
- Patient is taking a drug known to be a strong inhibitor or inducers of the isoenzyme CYP3A. Participants must be off a strong CYP3A inhibitors and inducers for at least two weeks prior to starting the study drug.
- Patient is taking a drug with known risk to promote QT prolongation and Torsade de Pointes
- Patient is currently using herbal preparations or medications. Participants should stop using herbal medications 7 days prior to the first dose of the study drug.

- Patient is using warfarin or any other Coumadin-derivative anticoagulant. Patients must be off Coumadin-derivative anticoagulants for at least seven days prior to starting the study drug. Low molecular weight heparin is allowed
- Patient has a history of allergic reactions to compounds of similar chemical or biological composition to buparlisib
- Patient has an uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, chronic liver disease, chronic renal disease, pancreatitis, chronic pulmonary disease, or psychiatric illness or social situations that would limit compliance with the study requirements
- Patient has acute viral hepatitis or a history of chronic or active HBV or HCV infection
- Patient has an active concurrent malignancy requiring active therapy.
- Patient is known to have human immunodeficiency virus (HIV) infection
- Patient has any severe psychiatric disease that would interfere with participation in the trial as determined by the study investigator
- Patient has ≥ CTCAE grade 3 anxiety
- Patient has ≥ CTCAE grade 2 diarrhea
- Patient has a score ≥12 on the PHQ-9 questionnaire
- Patient selects a response of “1, 2 or 3” to question number 9 on the PHQ-9-questionaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9).
- Patient has a GAD-7 mood scale score ≥15.
- Patient has a 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 (e.g. risk of doing harm to self or others).
- Patient has active cardiac disease or cardiac dysfunction including any of the following:
    - Left ventricular ejection fraction (LVEF) ,50% as determined by Multiple Gated Acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc>480msec on screening ECG (using the QTcF formula)
    - Angina pectoris that requires the use of anti-anginal medications
    - 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 documented compromise in cardiac function
    - Symptomatic pericarditis
    - Myocardial infarction within the last 6 months, documented by persistent elevated cardiac enzymes or persistent regional wall motion abnormalities on assessment of left ventricular ejection fraction function
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Congenital long QT syndrome
- Patient is currently receiving treatment with QT prolonging medication known to have a risk to induce Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug.
- Patient has impaired gastrointestinal function or gastrointestinal disease affecting absorption of buparlisib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive small bowel resection).

- Patient has poorly controlled diabetes mellitus with a glycosylated hemoglobin >8% or poorly controlled steroid-induced diabetes mellitus with a glycosylated hemoglobin of >8%.
- Patient underwent major systemic surgery ≤ 2 weeks prior to starting the trial treatment or who has not recovered from the side effects of such surgery.
- Women who are pregnant or nursing (lactating), where pregnancy is defined as a state of a female after conception until the termination of gestation, confirmed by a positive serum hCG laboratory test of > 5 mIU/mL.
- Patients who have received allogenic stem cell transplants.

6.3 Pregnancy and Reproduction

6.3.1 Women:

- 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 (i.e. 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 our without hysterectomy at least six weeks prior to enrollment in the study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up of 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 study treatment and for 16 weeks after study discontinuation. Highly effective contraception is defined as either
    - True abstinence: When this is the 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: Surgical bilateral oophorectomy, with or without hysterectomy, or tubal ligation at least six weeks prior to study enrollment. In the 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 appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients participating in 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 form/gel/film/cream/vaginal suppository

    NOTE: Oral contraception as well as injected, implanted, or local hormonal methods of contraception are not acceptable methods of contraception for women of child bearing potential as buparlisib potentially decreases the effectiveness of hormonal contraceptives

- Women of child-bearing potential must have a negative serum pregnancy test at screening

- In addition to having a negative pregnancy test confirmed at screening, all female participants of child bearing potential must have a negative serum pregnancy test confirmed within 48 hours prior to dosing with the study drug.

6.3.2 Men:

- Fertile males, defined as all male subjects physiologically capable of conceiving offspring, must use a condom during study treatment and for 16 weeks after study discontinuation and should not father a child in this period
- Female partner of a male study subject should use a highly effective method of contraception while the male partner is receiving the study agent and for 16 weeks after the final dose of the study therapy

6.2.1.3 Inclusion of women, minorities or other underrepresented populations

Buparlisib is not known to differentially affect subpopulations, including women, minorities, or other underrepresented groups. The eligibility and exclusion criteria are not expected to differentially impact recruitment or retention of these subpopulations.

7.0 RECRUITMENT PLAN

MSKCC has long been a center of clinical excellence in PCNSL and is a nationally renowned referral center for patient with PCNSL. Additionally, we will work closely with the MSKCC Lymphoma service to enroll patients with SCNSL. Patients will be recruited from the neurology and lymphoma clinics at Memorial Sloan-Kettering Cancer Center. All patients will be seen by an attending physician who is an investigator on the trial. All patients enrolled on the trial must sign written informed consent. There is no gender or racial restriction. If accrual is inadequately slow, then we will reach out and collaborate with other centers.

8.0 PRETREATMENT EVALUATION

8.1 General Requirements

All participant need to fulfill inclusion and exclusion criteria and have signed an informed consent form.

A complete history, vital signs (including blood pressure, pulse, respiratory rate, temperature, weight and height), physical, and neurological examination (to include documentation of the patients Karnofsky performance status; Appendix 6) and NANO score as well as neuro-imaging (including contrast-enhanced MRI/CT brain and total spine) and/or CSF evaluation (including cell count, total protein and glucose as well as cytology) confirming tumor progression will be performed on all patients. All patients will need a PET body and brain for staging purposes prior to study enrollment. The scans done prior to study entry documenting progression will be reviewed by the principal investigator. The baseline scan or CSF evaluation should be performed 21 days of registration. Prestudy laboratory tests need to included CBC with differential, platelets, coagulation panel (including PT, PTT, INR), sodium, potassium, calcium, AST, ALT, alkaline phosphatase, total bilirubin, fasting plasma glucose, creatinine, lipid panel, HbA1c, 8 hour fasting C-peptide, amylase, lipase, LDH, a screening hepatitis B and C serology, a screening HIV serology, serum pregnancy test for women of childbearing potential. Prestudy laboratory tests must be obtained within 21days of registration.

Documentation of tumor diagnosis. Following registration, slides from the most recent pre-registration biopsy and/or CSF cytology must be submitted for review and confirmation of diagnosis. Additionally, 20 unstained slides from the initial tissue diagnosis must be submitted for exploratory studies.

A contrast enhanced CT scan of the chest, abdomen and pelvis, ophthalmologic evaluation including slit lamp exam, 12-lead ECG, ECHO/MUGA, as well as a bone marrow aspirate must be performed for staging purposes. These staging tests must be obtained within 21 days of registration.

Patient need to complete the PHQ-9 and GAD7 self rating mood scale within 21 days of registration (see Appendix 6).

Please also see Table 6 for an overview of testing required prior to enrollment into the trial.

9.0 TREATMENT/INTERVENTION PLAN

All participant will initiate treatment at 100 mg Buparlisib PO within 96 hours of registration. The study drug will be administered with a flat-fixed dose, and not by body weight or body surface area. For the purpose of this trial a cycle will be defined as 28 days. There will be no breaks between dosing cycles. The study drug buparlisib will be self-administered. The investigator will instruct the participant to take the study drug exactly as specified in the protocol. Buparlisib will be administered on a continuous once daily schedule. Patients will be asked to keep a pill diary. Treatment will continue until one of the events in Section 13 occurs.

9.1 Dose Modifications/Delays

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug. If administration of buparlisib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to the rules described in Table 11. Any planned variance from these guidelines in the view of patient safety must be previously discussed with the sponsor unless there is an urgent need for action. Any changes in buparlisib administration must be recorded in the pill diary.

All dose modifications, interruptions, or discontinuations must be based on the worse preceding toxicity as graded using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE), which can be found on the website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. In the case of toxicity, appropriate medical treatment should be used, including anti-emetics, anti-diarrheals, etc.

All adverse events experienced by participants will be collected from the time of the first dose of study treatment through the study until the final study visit. Participants continuing to experience toxicity at the end of treatment visits may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

All participants will be initially treated at Dose Level 0. A buparlisib dose reduction will be administered at 20 mg below the current dose. The dose reduction steps are outlined in Table 5.

Table 5: Dose reduction steps for Buparlisib

Buparlisib dose levels and dose reductions*	
Starting dose level – 0	100 mg/day continuously
Dose level – 1	80 mg/day continuously
Dose level – 2	100 mg/day 5 days out of 7
Dose level – 3	60 mg/day continuously
Dose level – 4	80 mg/day 5 days out of 7

*Dose reduction should be based on the worst preceding toxicity

Table 11 should be adhered to for all toxicities as noted below, regardless of suspected attribution unless otherwise specifically noted within the table. For situations where a participant experiences a toxicity which the treating investigator feels is unrelated to treatment with buparlisib, but which requires a hold or reduction of the study drug according to Table 11, maintaining treatment with the study drug is allowable following discussion with the Principal Investigator.

When treatment must be held pending resolution of toxicity to grade 1 or return to baseline, and the toxicity is a lab abnormality, in cases where the participant had a pre-existing laboratory abnormality at baseline, the toxicity can be considered "resolved from a hold perspective when it has resolved to within 1 grade of the baseline value.

NOTE: For the purposes of data entry, value from screening assessments should be entered in as "baseline values." However, true "baseline values" for the purpose of dose modifications on study will be considered the last assessments or tests performed prior to initiation of study therapy.

Exception: In instances where the value within 1 grade of the baseline value would still require a hold, continue to hold until resolution of toxicity to grade 1 or return to baseline.

Participants who experience an adverse event that requires a treatment delay or dose reduction should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution.

Following a dose delay which resumes mid cycle, day 1 procedures not associated with the adverse event do not need to be repeated.

No more than 4 levels of dose reduction are permitted in this study. Participants cannot be treated below dose level -4. If a participant whose buparlisib dose has been reduced by 4 dose levels requires another dose reduction, treatment on study must be stopped unless the participant has benefited from the study, in which case the investigator will contact the Principal Investigator to determine if the participant will remain in the study.

A treatment delay of up to 28 days is permitted. If the toxicity has not resolved after a 4 week delay, the participant must be removed from study treatment unless the participant has benefited from the study, in which case, the investigator may contact the Principal Investigator to determine if the participant will remain in the study.

Dose re-escalation is never permitted in this study.

Cycle length will be 4 weeks (28 days), even if treatment is held for toxicity. There is no stopping in counting cycles/days for those periods where a subject's drug is withheld. All study evaluations and treatments should continue as if study treatment is not being held.

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed as outlined in Table 11 at least once a week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of buparlisib.

9.2 Treatment interruption and treatment discontinuation

If the study drug is being held due to toxicity, scheduled visits and all assessments should continue to be performed, with the exception of the dosing of the held study drug. If treatment with the study drug is withheld for ≥ 28 days, then the study drug must be permanently discontinued. Patients who permanently discontinue the study drug should have a follow up at approximately 30 days after discontinuation of all study treatment or resolution of the adverse event to ≤ grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 General Requirements

Table 6 describes the required procedures. All procedures may increase in frequency if clinically indicated or oriented following a toxicity/adverse event.

A complete history, vital signs (including blood pressure, pulse, respiratory rate, temperature, weight and height), physical and neurological examination (to include documentation of the patients Karnofsky performance status (Appendix 6) and NANO score as well as a serum pregnancy test for women of childbearing potential will be performed on day 1 (+/- 4 days) of each cycle.

Neuro-imaging (including contrast-enhanced MRI/CT brain and total spine) and/or CSF collection (for patients with CSF disease; through Ommaya or spinal tap; including cytology) will need to be performed on all patients on day 1 cycle 3, and each additional odd numbered cycle (+/- 4 days). Imaging will include only the side of active disease (MRI brain for patients with brain disease; MRI total spine for patients with intraspinal disease; MRI brain and total spine for patients with brain and spine disease as well as leptomeningeal disease) or sides suggested by new neurologic symptoms and signs. All MRI imaging will included MR perfusion . If MRI spectroscopy is additionally performed, we will collect the additional data.

CBC with differential, platelets, sodium, potassium, calcium, AST, ALT, alkaline phosphatase, total bilirubin, fasting plasma glucose, creatinine, will need to be performed at day 1 and day 15 of each cycle and at the end of the treatment (+/- 4 days).

Amylase and lipase need to be assessed at the end of the treatment (+/- 4 days).

Chest X-ray and 12-lead ECG need to be done every other cycle starting at day 1 of cycle 3 (+/- 4 days)

Participants need to complete the PHQ-9 and GAD7 self rating mood scale (see Appendix 6).at day 1 and day 15 of cycle 1 and 2. On each consecutive cycle only on day 1 and at the

end of treatment (+/- 4 days). Questionnaires can be performed over the phone on Cycle 2 Day 15 by research staff, if the participant is not able to physically attend to clinic.

Table 6: Required Activity Calendar

Tests and procedures	Screening	On trial					
	Prior to Registration	Cycle 1		Subsequent cycles		End of treatment	30-day post drug
		Day 1	Day 15	Day 1	Day 15		
Informed consent	X						
Inclusion/exclusion criteria	X						
History, Physical and neuroexam	X	X		X		X	X
Vital signs (blood pressure, pulse, respiration rate, temperature, height, weight) and KPS (Appendix 6)	X	X		X		X	X
Serum pregnancy test (if applicable)	X	X		X		X	
Adverse event assessment	X			X		X	X
Hematology group (CBC & diff)	X	X	X	X	X	X	
Chemistry group (Sodium, Potassium, Calcium, AST, ALT, Alk Phos, Total Bilirubin, Glucose, Creatinine)	X	X	X	X	X	X	
Fasting plasma glucose	X	X	X	X	X	X	
Coagulation (PT, PTT, INR)	X	X		X		X	
HbA1c	X						
8h fasting C-peptide	X						
Lipid panel	X			X*			
Amylase, lipase	X					X	
LDH	X						
Hepatitis B and C screen	X						
12-lead EKG	X			X$			
Chest X-ray				X$			
MUGA/ECHO	X						
HIV screen	X						
Bone marrow aspirate and biopsy	X						
PET brain and body	X						
PHQ-9 Patient self-rating mood scale	X		X	X	X (1)	X	
GAD7 Patient self-rating mood scale	X		X	X	X (1)	X	
NANO Score Assessment	X			X$		X	
Cerebrospinal fluid (CSF) Analysis including cytology	X			X(2)		X(2)	
Contrast-enhanced MRI/CT of the brain and total spine with perfusion	X			X(3)		X(3)	
Response evaluation				X (4)		X	
Computed tomography of chest, abdomen, pelvis	X						
Ophthalmologic evaluation including slit lamp exam	X						
PK BKM120 CSF			X(5)				
PK BKM120 Blood			X(6)				
Blood collection for genomic DNA			X				
Collection of archival FFPE tumor samples	X						X(7)

(1): PHQ-9 and GAD7 will be collected on day 15 of cycle 1 and day 1 and day 15 during cycle 2; then only on day 1 on subsequent cycles
(2): Collection on day1 of all odd cycles starting on cycle 3; for patients with CSF disease only; response to treatment will be measured in CSF (+/- 4 days)
(3): Imaging on day 1 of all odd cycles starting with cycle 3; MRI brain for patients with brain disease, MRI total spine for patients with intraspinal disease; MRI brain and total spine for patients with brain and spine disease as well as leptomeningeal disease (+/- 4 days)
(4): Response will be evaluated on day 1 of all odd cycles starting with cycle 3
(5): Patients with Ommaya reservoir: CSF collection at 1h, 2h, 4h after drug administration; no Ommaya: CSF collection through

lumbar puncture 2h after drug administration (+/- 30 min)
(6): Patients with Ommaya reservoir: Blood collect parallel to CSF collection at 1h, 2h, 4h after drug administration; no Ommaya: blood collection parallel to CSF collection through lumbar puncture 2h after drug administration (+/- 30 min)
(7): If there is a re-resection, FFPE material will be collected
* Every 3 cycles starting day 1 of cycle 3 (+/- 4 days);
$ Every other cycle starting at day 1 of cycle 3 (+/- 4 days)
% Every MRI Visit

10.2 Pharmacokinetic analysis and evaluation of study drug penetration into the CSF space

In phase I clinical trials with buparlisib, preliminary PK data showed that buparlisib accumulated ~3 fold in achieving steady state, consistent with an effective half-life of ~ 40 hours. Steady state can be reached after approximately 7-10 days of daily dosing in most participants.

On day 15 of cycle 1, patients will undergo CSF and plasma pharmacokinetic analysis. At day 15, the study drug has reached steady state. Patients with an Ommaya reservoir will undergo taps of their reservoir at 1h, 2h and 4h after drug administration. Patients without an Ommaya reservoir will undergo a single spinal tap at 2h after study drug administration. The patient will have plasma collection in parallel (patients with Ommaya reservoir: plasma collection at 1h, 2h, and 4h post drug administration; patients without Ommaya reservoir: plasma collection at 2h post drug administration. Each draw should be collected at +/- 30 min of each time point. CSF and plasma concentrations of the drug will be measured by liquid chromatography with tandem mass spectrometry to derive a CSF/plasma concentration. Samples will be stored in the Mellinghoff laboratory and analyzed at the end of the study.

10.3 End of treatment visit, including premature withdrawal and study safety follow up

All patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) 30 days after the last dose of study treatment. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed at least once a week for 4 weeks and subsequently at 4-weeks intervals until resolution or stabilization of the event, whichever comes first.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

10.4 Patient self-rating mood questionnaires

The Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) will be collected to screen patients for the study and to aid in the identification and severity assessment of potential mood alterations. The PHQ-9 and GAD-7 are validated (Kroenke 2001, Spitzer 2006, Spitzer 1999), patient self-administered questionnaires developed for use in clinical practices.

The PHQ-9 consists of 9 questions that assess anhedonia, depressed mood, sleep, energy, appetite, guilt and worthlessness, concentration, feeling slowed down or restlessness, and suicidal thoughts. For each of these questions, patients are asked to rate how much over the past 2 weeks they have been bothered by the symptom. Scoring of the PHQ-9 is based on a Likert-type scale from 0 to 3 (0

indicates not at all; 1, several days; 2, more than half the days; 3, nearly every day). The sum of all nine questions is used to determine a total PHQ-9 score ranging from 0 to 27.

The GAD-7 is a one-dimensional questionnaire consisting of 7 questions. Similarly to the PHQ-9, in the GAD-7, patients are asked to indicate how often, over the past 2 weeks, they have been bothered by each of the seven core symptoms of generalized anxiety disorder as referenced in the DSM IV. Response options are ‘‘not at all’’ ‘‘several days’’ ‘‘more than half the days’’ and ‘‘nearly every day’’ scored as 0, 1, 2, and 3, respectively. The sum of all seven questions calculates the total GAD-7 score. Therefore, GAD-7 scores range from 0 to 21.The patient must complete two different mood questionnaires, (PHQ-9 and GAD-7) at Screening, at collection on day-1 or within the screening, then on day 15 of cycle 1 and day 1 and 15 of cycle 2 and on day 1 of subsequent cycles, as well as at end of treatment. Additional assessments may be done according to the clinical judgment of the investigator. All questionnaires should be administered in the patient’s local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient’s perspective. This is to avoid potentially biasing patients or their responses to study questionnaires.

Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaires, this should be documented in study source records.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in section “safety monitoring and reporting” of this guidance document. The severity classification table described in Table 7 for the PHQ-9 and GAD-7 will be used in this study to increase the sensitivity of identifying potential anxiety and/or depression disorders. During the study, questionnaire scores and corresponding severity classification can be used to aid the investigator in identifying new or worsening of events. Importantly, grading must be based on the clinical interpretation of severity according to the NCI-CTCAE (v 4.03).

Table 7 Classification of severity based on mood questionnaire scores

PHQ-9 (depression)		**GAD-7 (anxiety)**	
Score	Severity	Score	Severity
0-4	None	0-4	None
5-9	Mild	5-9	Mild
10-19	Moderate	10-14	Moderate
20-27	Severe	≥ 15	Severe

At Screening, a patient may be judged by the investigator or a psychiatrist to be ineligible based on medical mental health history as listed in the exclusion criteria. Alternatively, patients who score ≥ 12 on the PHQ-9 or ≥ 15 on the GAD-7 mood

scale, respectively, or select a positive response of '1, 2, or 3' to question number 9 regarding suicidal thoughts or ideation will be excluded from the study.

During the treatment phase, patients who indicate a positive response by selecting '1, 2, or 3' to question number 9 in the PHQ-9 must omit treatment with study drug buparlisib and must be referred for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient PHQ-9 self-assessment.

Investigators must not encourage the patients to change responses reported in questionnaires. Guidelines on how to instruct the patient to complete the questionnaires as well as how to determine the scores will be provided with each instrument. Guidance on scoring questionnaires is also provided in Appendix 5. Dosing modification guidelines for buparlisib are provided in Table 11. For additional information on AE reporting, please refer to Section Safety monitoring and reporting.

10.5 Correlative/special studies

Correlative studies are mandatory for all participants.

10.5.1 Correlation of drug response to PI3K pathway activation status

For pathway response studies we will assess activation of the PI3K pathway members in archival FFPE tissue. Previous studies and our own data have demonstrated the reliability of pathway members pAKT, pS6, and p4EBP1 in readouts of pathway modulation. The level of PI3K pathway activation will be determined by semi-quantitative immunohistochemical scoring for pAKT, pS6, and p4EBP1. All pathway modulation scores will be correlated with response to study drug. The studies will be performed in the Mellinghoff laboratory (MSKCC).

10.5.2 Characterization of mutational abnormalities

Participants tumor tissue will be assess for mutational abnormalities, DNA will be extracted from FFPE tumor tissue. We will also collect germline DNA from whole blood collection (See 10.5.5). DNA extraction, quantification, and quality control will be performed according to established protocols in the Mellinghoff laboratory. Through target sequencing using the Miseq technology (performed at the MSKCC Geoffrey Beene Translational Oncology facility) mutational abnormalities including but not limited to CD79a, CD79b, PIK3Ca, PIK2CB, PIK3CD, MYD88, CARD11, and TNFAIP2 will be assessed and correlated with response to study drug treatment.

10.5.3 Correlation of MR spectroscopy changes to buparlisib as a potential biomarker

Research on cancer metabolism has identified a link between deregulated signaling pathways and altered cellular metabolism. These changes in cancer cell metabolism can be measured by magnetic resonance spectroscopy (MRS) and might serve as a possible biomarker of therapeutic effect. Using ^{1}H MRS in orthotopic glioblastoma models, Koul et al (2010) have demonstrated that inhibition of the PI3K pathway results in a decrease in total choline-containing metabolite levels, composed of choline, phosphocholine, and glycerophosphocholine. Therefore ^{1}H MRS could be used as a powerful tool to probe the change in cellular metabolism before and after initiation of study drug.

10.5.4 Correlation of ADC/DWI/perfusion MRI imaging to changes to buparlisib

ADC signal on MRI is inversely correlated with cell density in PCNSL. Therefore a high ADC correlates with a low cell number and was associated with better outcome (Barajas, 2009). We want to further investigate MRI changes in ADC, DWI, and perfusion imaging in response to study drug and PI3K pathway inhibition and plan to correlate MR imaging changes with clinical outcome.

10.5.5 Germline DNA collection

Whole blood will be collected on cycle 1 day 15 (+/- 4 days). Blood will be collected in an K2EDTA containing blood collection tube (lavender top tube). Blood will be stored in the Mellinghoff lab prior to DNA isolation.

11.0 TOXICITIES/SIDE EFFECTS

11.1. Anticipated toxicities

In order for an event to be expected (known correlation to the study drug) for the purposes of adverse event reporting, the event must be included in this section.

A list of adverse events of all grades suspected to be buparlisib treatment related in phase I studies, organized by CTCAE v4.0 category includes:

- Cardiovascular: Hypertension
- Gastrointestinal: Diarrhea, dyspepsia, mucosal inflammation, nausea
- General disorders: Asthenia, fatigue, pyrexia
- Investigations: Aminotransferase elevation/transaminitis, GGT elevation, hyperbilirubinemia, lymphopenia, elevated lipase
- Metabolism and nutritional disorders: Hyperglycemia, hypophosphatemia, anorexia
- Nervous system disorders: Dizziness
- Psychiatric disorders: Mood alterations including depression and anxiety
- Pulmonary: Pneumonitis
- Skin: Rash, pruritis.

The safety experience for single agent buparlisib in trial CBKM120X2101 is summarized in Table 10

Table 10: Most frequent Adverse Event (≥15%) related to study drug in study CBKM120X2101 (n=81)

Event	All grades	Grade 3/4
Fatigue/asthenia	31 (38.3%)	3 (3.7%)
Decreased appetite	24 (29.6%)	-
Diarrhea	24 (29.6%)	3 (3.7%)
Hyperglycemia	24 (29.6%)	4 (4.9%)
Nausea	24 (29.6%)	-
Rash	22 (27.2%)	4 (4.9%)
Mood altered/emotional disorder/affective disorder	17 (21%)	4 (4.9%)
Transaminases increased	16 (19.8)	9 (11.1%)
Anxiety	14 (17.3%)	1 (1.2%)
Depression	14 (17.3%)	1 (1.2%)

11.2 Toxicity Management

Routine supportive care is recommended. Routine prophylactic use of G-CSF is not permitted. Please refer to Table 11 for toxicity specific modifications.

Table 11: Criteria for interruption and re-initiation of buparlisib treatment

Worst toxicity (CTCAE 4.03 Grade)**	**Dose Modifications for Buparlisib**
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a **single** temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
RENAL	
Serum creatinine	
Grade 1 (< 2 x ULN)	Maintain dose level
Grade 2 (2 – 3 x ULN)	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from buparlisib
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from buparlisib
HEPATIC	
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from buparlisib
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from buparlisib
AST or ALT	
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level with LFTs* monitored per protocol

Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Can continue treatment at ↓ 1 dose level
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level** If no recovery in ≤28 days, discontinue buparlisib permanently
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Discontinue buparlisib permanently
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue buparlisib***

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

**In case of recurring Grade 3 or higher toxicity after re-challenge, patient should be permanently discontinued

***All patients with ALT or AST>3.0x ULN and total bilirubin >2.0x ULN in the absence of cholestasis must immediately be withdrawn from buparlisib and every attempt should be made to carry out the liver event follow-up assessments as described below in section 11.11.1.2**: Management of Hepatotoxicity (ALT and/or AST> 3.0x ULN and total bilirubin >2.0x ULN) in patients receiving buparlisib** and **Viral Serology and other tests for hepatotoxicity follow-up.**

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

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

Cycle 3 and onward: monthly or more frequently if clinically indicated

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

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

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

ENDOCRINE/METABOLIC	
Fasting Plasma Glucose (FPG)	
Grade 1 (> ULN - 160 mg/dL) (> ULN - 8.9 mmol/L)	Maintain dose level, check FPG every week ● initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion ● instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ● consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications), ● check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Grade 2 (>160 - 250 mg/dL) (> 8.9 - 13.9 mmol/L)	● If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), manage as for Grade 3 hyperglycemia (see below) ● If asymptomatic, maintain dose and re-check FPG

	within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2: ○ maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1 ○ initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if not improvement after several days. ○ instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ○ if FPG does not resolve to ≤ Grade 1 within 14 days after institution of appropriate anti-diabetic treatment reduce buparlisib by 1 dose level ● Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Grade 3 (> 250 - 500 mg/dL) (> 13.9 - 27.8 mmol/L)	Omit buparlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 3: ● administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate ● continue to omit buparlisib ● monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 ● If FPG resolves to ≤ Grade 1 in 7 days or less, then re-start buparlisib and ↓ 1 dose level ● If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from buparlisib ● initiate or continue anti-diabetic treatment as appropriate ○ instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ○ consider use of oral anti-hyperglycemic therapy such as metformin ● check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit buparlisib and following guidance for management of Grade 3 fasting plasma glucose (FPG)
Grade 4 (> 500 mg/dL) (≥ 27.8 mmol/L)	Immediately omit buparlisib, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4: ● administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate ● discontinue patient from buparlisib

	● instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study ● consider use of oral anti-hyperglycemic therapy such as metformin ● check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue buparlisib and following guidance for management of Grade 4 fasting plasma glucose (FPG).
CARDIAC	
Cardiac - Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue buparlisib with caution Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	● Omit buparlisib until resolved* (as defined below), then ↓ 1 dose level ● LVEF measurement to be repeated, if not resolved* within 21 days, permanently discontinue patient from buparlisib treatment
Refractory or poorly controlled, ejection fraction < 20%	● Permanently discontinue patient from buparlisib
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.	
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	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 or >60ms from baseline ● If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input. ● Once QTcF prolongation has resolved, buparlisib may be restarted at a one lower dose level Second Occurrence: ● Permanently discontinue patient from buparlisib
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from buparlisib
OTHER	
Mood alteration/Psychiatric Disorders	
* Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1",	

"2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.	
Grade 1*	● Maintain dose level ● Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation)
Grade 2*	● Omit dose until resolved to ≤ Grade 1 or baseline status ● Consider psychiatric consultation at the investigator's discretion and introduce optimal management (e.g. as per local guidelines and/or psychiatric/expert consultation) ● First event: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then maintain the dose level ● Second and further events: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then ↓ 1 dose level
Grade 3*	Omit dose until resolved to ≤ Grade 1 or baseline status ● Psychiatric consultation is required and introduce optimal management ● if the condition resolved to Grade ≤1 or to baseline status, continue to co-medicate and then ↓ 1 dose level
Grade 4*	Permanently discontinue patient from buparlisib ● Psychiatric consultation is required ● Introduce optimal management (e.g. as per local guidelines)
Rash	
Grade 1	Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 2	First occurrence: Omit dose until resolved to grade ≤ 1 then: ● If resolved in ≤ 2 weeks, maintain dose level. ● If resolved in more than 2 weeks, ↓ 1 dose level. Second occurrence: ↓ 1 dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 3	First occurrence: omit dose until resolved to CTCAE Grade ≤ 1; then ↓ 1 dose level. Second occurrence: permanently discontinue patient from buparlisib. Consider referral to dermatologist and manage rash per dermatologist's recommendation. According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.
Grade 4	Permanently discontinue patient from buparlisib. Consider referral to dermatologist and manage rash per dermatologist's recommendation. According to the investigators discretion, a paired skin

	biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then: ● If resolved in ≤ 7 days, maintain dose level ● If resolved in > 7 days, ↓ 1 dose level
Pneumonitis	**please see section for additional follow up for selected toxicities**
Other non- hematological adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from buparlisib ***Note:*** Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic
Stomatitis/Oral mucositis	
Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash (see also section for additional follow up for selected toxicities)
Intolerable Grade 2 or Grade 3	First occurrence: hold until resolved to grade ≤ G1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until resolved to grade ≤ G1 and ↓ 1 dose level.
Grade 4	Permanently discontinue patient from buparlisib.
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.	

11.3 Management of Pneumonitis in patients receiving Buparlisib

All patients participating in clinical trials with buparlisib will be routinely asked about and observed for the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). Additionally, chest X-rays will be performed every other cycle to further assess the development of pneumonitis. CT scans and pulmonary function tests should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed pneumonitis. In case of a documented pneumonitis, the guidelines (including dose modifications) in Table 12 should be followed. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment.

Table 12 Management of Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Buparlisib Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks, (or as per local practice) until return to within normal limits.	No specific therapy is required	Administer 100% of Buparlisib dose.

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Buparlisib Dose Adjustment
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 8 weeks, (or as per local practice) until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce buparlisib dose by 1 dose level (see Table 5) until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1 within 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks, (or as per local practice) until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with buparlisib until recovery to ≤ Grade 1. May restart study treatment within 28 days at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks, (or as per local practice) until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with buparlisib.

11.4 Guidelines for the treatment of buparlisib induced hyperglycemia

Buparlisib may affect glucose homeostasis which could result in increases of plasma glucose and insulin levels. Optimal glucose control should be achieved before starting a patient on study treatment and patients requiring insulin should be treated with caution. Patients with hyperglycemia should be instructed to follow dietary guidelines provided by the American Diabetes Association. They may also need to initiate, continue or intensify medication with appropriate anti-diabetic treatment including insulin or oral agents. (Note: some oral antidiabetic drugs are CYP2C9 substrate and should be used with caution; others are CYP3A inducers or inhibitors and are prohibited; See Appendix 1 and Appendix 2, respectively, for more details). Patients who develop Grade 3 or 4 hyperglycemia should be managed urgently as per standard clinical practice, with the goal of stabilizing glycemic control within 24 hours.

11.5 Guidelines for the treatment of study drug induced stomatitis/oral mucositis

General guidance and management include patient awareness and early intervention.

Evaluation for herpes virus or fungal infection should be considered.

Patients should be informed about the possibility of developing mouth ulcers/ oral mucositis and instructed to report promptly any signs or symptoms to their physician, Patients should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients

cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®), or as per local practice.

- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with buparlisib metabolism.

11.6 Guidelines for the treatment of buparlisib induced diarrhea

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Concomitant medication for the treatment of diarrhea should be considered, as per local practice and best investigator's judgment and may consist for example, as per "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson 2004), of loperamide given at a standard dose (e.g. initial administration of 4mg, then 2mg every 4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures could be considered for Grade 1-2 diarrhea. More severe diarrhea should be treated appropriately according to investigator discretion, including for example IV fluids.

Dose adaptations of buparlisib in case of treatment related diarrhea should follow the guidelines presented above for other non-hematological adverse events.

11.7 Guidelines for the treatment of buparlisib induced psychiatric disorders

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

For patients who experience new or worsening of existing psychiatric AEs of Grade ≥1, psychiatric consultation should be considered as described in Table 11.

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

If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit treatment with buparlisib and refer the patient for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment. During the study, subjects will be monitored at regular scheduled visits (e.g., Day 15 of Cycle 1, Day 1 and Day 15 of each subsequent cycle, and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self-reported questionnaires. Additional assessments may be done according to the clinical judgment of the investigator if desired.

11.8 Guidelines for the treatment of study drug induced skin toxicity

Close monitoring of potential skin reactions is recommended at each planned visit and should be recorded be reported as adverse event.

Although preclinical experiments demonstrated that buparlisib has no potential phototoxic effect, it is recommended to caution patients to avoid sun exposure during treatment with buparlisib, especially when they already have experienced rash or other skin toxicities. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the use of hats, long-sleeve shirts and long pants when outdoors.

11.9 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted (see Section Permitted concomitant therapy), except as specifically prohibited (see Section Prohibited concomitant therapy).

All medications (excluding study treatment and prior antineoplastic treatments), procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered within 28 days prior to the administration of buparlisib through 30 days after the last dose of buparlisib will be recorded in the Concomitant medications. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications (prohibited, see Section below) and food or vitamin supplements. The investigator should instruct the patient to notify the investigational site about any new medications she takes after the start of the study drug.

The patient must be told to notify the investigational 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 physical therapy and blood transfusions) administered during the study must be listed on the Concomitant Medications Sheet.

11.10 Permitted concomitant therapy

11.10.1 Corticosteroids

Corticosteroids may be used a limited doses, as they have limited impact on buparlisib metabolism. We recommend using corticosteroids at the smallest possible dose to control symptoms or cerebral edema and mass effect, and discontinue if possible. Please also refer to the Investigator‘s Brochure for the latest recommendations and findings.

Caution is also warranted for potential interaction with hyperglycemia.

11.10.2 Drugs that are metabolized by CYP450 enzymes

In vitro metabolism studies performed to examine the reversible and metabolism-dependent inhibition of CYPP450 enzymes showed that buparlisib is a weak, reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9 and CPY2C19. Note that with the data available, it is not possible 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 monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate.

Refer to Appendix 2: List of CYP450 substrates to be used with caution. Particularly, caution is advised when buparlisib is co-administered with drugs that are sensitive substrates and/or have a narrow therapeutic index (e.g., SSRI).

Concomitant treatment of buparlisib with weak or moderate inducers of CYP3A4 is permitted, however, duration of concomitant treatment should be kept as short as possible (e.g., less than 1 week), or fully avoided whenever possible. Note that coadministration of buparlisib with strong inducers is prohibited (see below).

11.10.3 Non-enzyme Inducing Anti-epileptic drugs

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed, except for those listed in Appendix 1.

11.10.4 Bisphosphonates

The use of bisphosphonates for bone metastatic disease is allowed.

11.10.5 Palliative radiotherapy

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Radiation to the central nervous system is NOT allowed during the trial. If a patient required palliative radiation involving the CSF space (vertebral spine radiation) prior authorization through the principal investigator is needed. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease. No dose modification of study treatment is needed during radiotherapy but should be monitored with caution.

11.10.6 Drugs with a conditional or possible risk to induce Torsades de Pointes

If a patient, after enrollment in the study, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for Torsades de Pointes included in Appendix 4, then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be closely monitored.

11.10.7 Gastric protection agents

Buparlisib is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract may alter the solubility of buparlisib and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H_2-antagonists (e.g., ranitidine) and antacids. Buparlisib should be dosed in a staggered manner at least 1 hour before or 10 hours after dosing with medicinal products that may alter the pH of the upper GI tract.

11.10.8 Prohibited concomitant therapy

11.10.8.1 Other anticancer therapy

Anticancer therapy (chemotherapy, endocrine, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is enrolled in the treatment portion of the trial. If such agents are required for a patient then the patient must be permanently discontinued from the treatment portion of the study.

11.10.8.2 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

11.10.8.3 Hematopoietic growth factors

Prophylactic use of hematopoietic growth factors (e.g. erythropoietins, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GMCSF)) are not permitted. However, in the event of an emergency (e.g. acute myelosuppression with infection), a patient may be given hematopoietic growth factors according to the investigator's judgment, and the sponsor should be notified as soon as possible. Subsequent secondary prevention use is permitted at investigator's discretion.

Patients who begin erythropoietin or darbepoetin therapy before randomization may continue this treatment at the discretion of the investigator.

11.10.8.4 Warfarin and coumarin derivatives

Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulants are not permitted.

Buparlisib is a weak inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. Despite the fact that the inhibitory signal was weak, an increase of 40-50% of warfarin exposure is possible and for a drug like warfarin, this might be clinically relevant.

11.10.8.5 Enzyme-inducing anti-epileptic drug (EIAED)

Use of enzyme-inducing anti-epileptic drug (EIAED) is not permitted. Refer to Appendix 1 for a list of prohibited EIAED.

If a patient is currently taking EIAED, they must have discontinued the EIAED therapy for at least two weeks prior to starting study drug.

If a patient is previously on a non-EIAED and needs to permanently change the anticonvulsant agent, but cannot change to another non-EIAED, the patient will be taken off buparlisib.

11.10.8.6 Drugs with a known risk for Torsades de Pointes

If a patient requires the concomitant use of any medication included in Appendix 3 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 Torsade de Pointes), study treatment must be delayed. Note that Appendix 3 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow therapeutic index) with a possible or conditional risk for TdP. Study treatment administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.

11.10.8.7 Moderate and strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of buparlisib is predominantly mediated by CYP3A4 and UGT1A4. Coadministration of buparlisib with strong and moderate CYP3A4 inhibitors and inducers is predicted to respectively increase or decrease the systemic exposure to buparlisib.

Please refer to Appendix 1 for a list of prohibited drugs. Please note that this list may not be comprehensive.

11.10.8.8 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. 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 at least 7 days prior to first dose of study treatment.

11.10.8.9 Hormonal contraception

Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving buparlisib.

11.11 Liver Toxicity

11.11.1 Liver Toxicity Findings

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

Approximately 25 to 45% of patients treated with single agent BKM120 reported liver toxicity (all grades, regardless of study drug relationship, 100 mg/d dose) based on a search of multiple MedDRA event terms (e.g. SMQ preferred terms). The incidence of grade 3 and 4 events was approximately 10 to 30%. Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly transaminase enzyme increases (ALT and/or AST). Data suggest a slightly higher rate of grade 3 and 4 liver enzyme elevations in Japanese patients (44%) in the [CBKM120X1101] study, however, the number of patients treated at 100 mg in this study was limited (n=9). Transaminase elevations typically occur during the first 6 to 8 weeks of treatment start.

Although transaminase increases are relatively common, only a few of the patients had other simultaneous observations related to impaired liver function (e.g. bilirubin increase or clinical symptoms).

Based on these findings, conservative inclusion criteria and guidelines to monitor and follow patients with LFT alterations (including dose and schedule modifications) have been implemented. Please refer to the respective inclusion/exclusion criteria and Table 11.0 in this protocol for more detailed guidelines.

11.11.1.2 Management of Hepatotoxicity (ALT and/or AST ≥ 3.0x ULN and total bilirubin ≥2.0x ULN) in patients receiving Buparlisib

Criteria for interruption and re-initiation of buparlisib treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in Section 11.2, Toxicity Management (Table 11).

Patients with clinically significant liver test abnormalities should perform liver-directed medical history, physical examination and other tests as medically indicated to assess potential relationship with study treatment and rule out other underlying causes (e.g. disease progression/obstruction, infection/hepatitis or other liver diseases, sepsis, metabolic diseases including diabetes, concomitant medications including herbals, alcohol, drug-drug interaction, cardiovascular disease/ischemia, other organ injuries, etc.). Any pre-existing liver conditions or risk factors should be reported in the respective medical history and concomitant medication CRF pages (if not done already).

All patients with ALT or AST >3.0 x ULN and total bilirubin > 2.0 x ULN in the absence of cholestasis (elevation of ALP in patients without bone metastasis or if bone metastasis are present elevation of 5'-nucleotidase and ALP liver fraction) must be immediately withdrawn from buparlisib, and every attempt should be made to carry out locally the liver event follow-up assessments as described below:

- Inform the sponsor about the event immediately after its occurrence by reporting the event immediately in the clinical database if it meets the criteria for an AE or SAE.
- Evaluate if associated with the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, or other organ involvement.
- Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.
- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease including metastasis or new lesions, obstruction/compression, etc.
- Perform viral hepatitis and other serology tests::
  - Hepatitis C (HCV) serology and viral RNA, Hepatitis B (HBV) serology and viral DNA, Hepatitis A (HAV) Immunoglobulin M (IgM) and HAV total
  - Hepatitis E (HEV) serology: IgM and IgG, viral RNA
  - Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Epstein-Barr viral (EBV) serology
- Verify and record the use of concomitant medications, acetaminophen, herbal remedies, and other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Consultation with a specialist(s) or a hepatologist(s) is recommended.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury
- LFTs should be followed-up weekly until resolve to ≤ grade 1, baseline or stabilization (no CTCAE grade change over 4 weeks) and outcome documented on the respective AE and lab chemistry pages.

11.11.1.3 Laboratory Evaluations

Hepatotoxicity follow-up testing will be performed when needed (refer to section

11.11.1.2) in patients receiving buparlisib.

Table 13 Clinical laboratory parameters collection plan

Test Category	Test Name
*Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up *	HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb, ALP, CPK, LDH, WBC (eosinophilia), and others.
* Hepatotoxicity follow-up testing/procedures will be performed locally (refer to Section 11.11.1.2: **Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving buparlisib** and **Viral hepatitis serology and other tests for hepatotoxicity follow-up**.	

Viral Hepatitis serology and other tests for hepatotoxicity follow-up
Viral hepatitis serologic tests are performed confirm patient's eligibility when needed per clinical judgment and specific patient's clinical circumstances.

During study treatment, viral hepatitis serologic and other tests will be performed as per the guidelines of management of hepatotoxicity (ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN) in patients receiving buparlisib, refer to Section 6.2.4.X Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving buparlisib for details.

Viral hepatitis serology includes the following:

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

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

Additional viral serology tests may include:

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

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Definitions of response

This study will use the Macdonald criteria (Macdonald, et al. 1990). Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the non-enhancing component, should be performed. As with the Macdonald criteria (Macdonald, et al. 1990), the product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

a. Measurable disease: Measurable lesions are defined as enhancing lesions that can be accurately measured in at least two dimensions ≥ 10mm. All tumor measurements must be reported in millimeters.
b. Non-measurable disease: All other lesions (or sites of disease), including small lesions (<10mm with conventional techniques) are considered non-measurable disease.
c. Cytologic Complete Response (CCR): Complete clearing of all malignant cells from ventricular or lumbar source based on cytology. A cytologic CR must be documented by two negative cytologies from ventricular or lumbar sources on consecutive occasions at least 4 weeks apart.

12.2 Guidelines for evaluation of measurable disease

1. Complete Response (CR): Complete disappearance of all measurable and non-measurable disease. No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. Patients must be on no steroids.
2. Partial Response (PR): Greater than or equal to 50% decrease over the baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of non-measurable disease. No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.
3. Stable/no response: Does not qualify for CR, PR, or progression. All measurable and non-measurable sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.
4. Progression: 25% increase in the sum of products of all measurable lesions over smallest sum observed (or baseline if no decrease) using the same techniques as baseline, OR clear worsening of any non-measurable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

12.3 Guidelines for patients with CSF disease

1. Complete Response (CR): Combination of CCR and complete disappearance of all measurable and non-measurable disease (if the participant had imaging abnormalities at enrollment). No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. Patients must be on no steroids.
2. Partial Response (PR): Combination of CCR and stable size of all measurable and non-measurable disease (if the participant had imaging abnormalities at enrollment). No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. Patients should be on a stable or reduced does of steroids.
3. Stable/no response: Tumor cells still present in CSF cytology and stable size of all measurable and non-measurable disease (if the participant had imaging abnormalities at enrollment). No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. Patients should be on a stable or reduced does of steroids.

4. Progressive Disease (PD): 25% increase in the sum of products of all measurable lesions over smallest sum observed (or baseline if no decrease) using the same techniques as baseline, OR clear worsening of any non-measurable disease, OR appearance of any new lesion/site on imaging, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer) regardless of CSF cytology status.

12.4 Best response and objective response rate (ORR)

For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to section 12.2/12.3. If the response does not persist at the next regular scheduled MRI/CT, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e.g. still present on the subsequent MRI/CT, it will be recorded as a sustained response, lasting until the time of tumor progression.

The objective response rate (ORR) is defined as the portion of patients with a best response of CR plus PR according to section 12.2/12.3divided by the total number of patients included in the study.

12.5 Neurological exam

Although not used for determining response, it is useful to evaluate changes in the neurological exam compared to the previous exam. The following scale may be used:

+2	Definitely better
+1	Possibly better
0	Unchanged
-1	Possibly worse
-2	Definitely worse

Additionally the participant will be evaluated for neurologic functioning by the investigator and according to the NANO scale (). Assessments will be performed at baseline and will each treatment response assessment (every MRI visit). The NANO is an objective, quick, user-friendly and quantifiable evaluation of nine major domains for subjects with brain tumors. The domains include: gait, strength, ataxia, sensation, visual field, facial strength, language, level of consciousness, behavior and overall. Each domain is rated on a scale of 0 to 3 where 0 represents normal and 3 represents the worst severity. A given domain should be scored non-evaluable if it cannot be accurately assessed due to pre-existing conditions, co-morbid events and/or concurrent medications. The evaluation is based on direct observation/testing performed during routine office visits. The NANO scale will be completed by the investigator or designated study physician prior to day 1 cycle 1 (baseline) and then with each MRI).

12.6 Performance status

Participants will be graded according to Karnofsky Performance Status Scale (KPS) (Appendix 6).

12.7 Overall survival time (OS)

Overall survival time (OS) is defined as the time from treatment start to the date of death due to any cause. Patients not known to have died will be censored at the time of their last available assessment or at the analysis cut-off whichever comes earlier.

OS will be described using Kaplan-Meier curves with appropriate summary statistics.

12.8 Progression-free survival (PFS)

Progression-free survival (PFS) is defined as the time from the date of treatment start to the date of the first documented PD or death due to any cause. If a patient is not known to have progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off date and before the anti-cancer therapy date. PFS will be based on the investigator's assessment of MRI, CSF studies and clinical presentation.

PFS will be described using Kaplan-Meier curves with appropriate summary statistics. Additionally, we will report PFS at 12 weeks (PFS12w), PFS at 24 weeks (PFS24w) and at 48 weeks (PFS48w).

12.9 Duration of response

Duration of response is defined as the time from the date of first occurrence of CR or PR to the date of the first documented PD or death due to any cause. If a patient is not known to have progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, duration of response is censored at the time of the last tumor assessment before the cut-off date and before the anti-cancer therapy date.

Duration of response will be described using Kaplan-Meier curves with appropriate summary statistics.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. The absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevent further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

The participant will be removed from study treatment when any one of the criteria listed above applies. The reason for study treatment removal and the date the participant was removed must be documented in the study-specific case report form. Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, investigators must immediately notify the Principal Investigator.

Patients will be treated until disease progression, death, unacceptable toxicity or other discontinuation criteria are met.

After patients are removed from the trial they will represent after 30 days for a clinical follow-up visit. Thereafter, they will be followed for 12 months. The frequency of clinical follow-up visits is at the discretion of the investigator but we recommend a frequency of every 3-4 months. Thereafter, patients will be contacted over the telephone once a year.

14.0 BIOSTATISTICS

As outlined in Table 1 Section 3, prior trials in patients with recurrent PCNSL have observed PFS6m of 35-45% with conventional chemotherapy regimens. The primary objective of this phase II study is to assess the efficacy of the targeted therapy buparlisib. PFS24w rate of patients receiving buparlisib will be estimated along with a 95% confidence interval. Progression-free survival at 24 weeks (PFS24w) is defined as the percentage of patients that have not developed progression of disease or died without progression at 24 weeks from the start of treatment. All patients will be followed for 6 months.

Twenty-one patients will be entered in this trial with an anticipated accrual rate of 1-2/months. The therapy will be considered worth pursuing if ≥12 out of 21 participants are progression free at 6 months (lower bound of the 95% confidence interval exceeds 34%, the approximate PFS24w rate with conventional chemotherapy).

Based on an accrual of 21 participants, two-sided 95% binominal confidence intervals for a range of overall response rate are as follows:

Table 14: Two-sided 95% binominal confidence intervals

Number of participants with overall response:		6	8	10	12	14	16
Point estimate of overall response rate:		29%	38%	48%	57%	67%	76%
Two-sided 95% confidence interval (exact binominal):	lower	11.28%	18.11%	25.71%	34.02%	43.03%	52.83%
	upper	52.18%	61.56%	70.22%	78.18%	85.41%	91.78%

In the unlikely event a patient is lost to follow-up before assessment of the primary endpoint he or she will be considered an event in the analysis of the primary endpoint.

In addition to PFS24w, we will assess progression-free survival at 12 weeks and 48 weeks (PFS12w and PFS48w). PFS12w/PFS48w is defined as the percentage of patients that have not developed progression of disease or died without progression at 3/12 months from the start of treatment. PFS12w and PFS48w rates of patients receiving buparlisib will be estimated along with a 95% confidence interval. The PFS12w will be assessed based on the

imaging and/or CSF assessment at day 1 cycle 3. PFS24w will be based on the imaging and/or CSF assessment at day 1 cycle 6, and PFS48w on imaging and/or CSF assessment at day 1 cycle 12.

Frequencies of toxicities will be summarized based on the Common Toxicity Criteria version 4.0. Adverse events that occur will be reported for and described in terms of incidence and severity. Objective response rate (defined as proportion of patients who achieve a complete and partial response among all patients) will be estimated along with a 95% confidence interval. For patients who respond to treatment (complete or partial response), duration of response will be calculated from the date of response to the date of progression of disease. Patients still responding at date of last follow-up will be censored. Overall survival will be calculated as the time from the start of treatment to the date of death or last follow-up. Overall survival and duration of response will be calculated using Kaplan-Meier methodology.

Pharmacokinetic parameters including half-life, C_{max}, AUC, volume of distribution, and clearance will be determined using non-compartmental methods via WinNonlin (Pharsight, Mountain View, CA). Standard descriptive statistics (mean, standard deviation, median, range) will be presented on all parameters for both serum and CSF samples.

Mutational abnormalities (mutant or not) will be assessed for the following genes: A20, CARD11, CD79B, PIK3CA, PIK3CD and MYD88. Additionally, the phosphorylation status of the following members of the PI3K pathway will be assess through immunohistochemical staining (activated or not activated). Both, mutational abnormalities as well as immunohistochemical status will be cross tabulated with patient outcomes such as PFS24w and ORR. Associations will be assessed using Fishers exact test. For patients who receive MR spectroscopy peak values will be described and graphically presented through course of treatment. Perfusion data (ADC value categorized as high versus low) will be correlated with patient outcome if data permit.

The evaluation of NANO will be measured by the distribution of change from baseline in the level of function score for each domain.

It is anticipated that 1-2 patients per month will be accrued to this study and the study will be completed within 2 years. Accrual is limited to 10 patients with SCNSL and 11 patients with PCNSL.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 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.

15.2 Randomization

Not applicable in this study

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator/Data Manager will be assigned to the study. The responsibility of the Clinical Research Coordinator/Data Manager 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 MSKCC secure database, CRDB.

16.1 Quality Assurance

This study will utilize the MSKCC's Clinical Research Management Office, and will adhere to all regulatory and data management polices accordingly. Monthly 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-ups 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 samples 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.

16.2 Data and Safety Monitoring

The trial will utilize the MSKCC's Data Safety Monitoring Plan. The plan addressed the issues set forth by the NCI in the document entitled "Policies of the National Cancer Institute for Data and Safety Monitoring in Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html.

The MSKCC DSM Plan can be found at:

http://onemsk/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

MSKCC DSM Plan has been designed to ensure that all clinical trials implemented at our center are monitored, and that reporting techniques fulfill sponsor, institutional, and governmental requirements.

17.0 PROTECTION OF HUMAN SUBJECTS

The patient (or insurer) will be charged for all costs associated with this protocol except cost of the study drug Buparlisib (BMK120) and exploratory analyses conducted following registration.

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.

17.2.1 Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days 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 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department (fax # 877-778-9739).

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, 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 treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) 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.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 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 Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Overdoses

Any overdose, even in the absence of a resulting AE, must be forwarded to Novartis and reported to the Principal Investigator.

Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the Investigators' Brochure. Additional safety information collected between updates of the Investigators' Brochure will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

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 1: List of prohibited CYP3A inhibitors and inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	amprenavir	carbamazepine *	felbamate *
conivaptan	aprepitant	phenobarbital *	topiramate * (>200 mg/day)
indinavir	atazanavir	phenytoin *	oxcarbazepin *
itraconazole	cimetidine	fosphenytoin *	eslicarbazepin *
ketoconazole	ciprofloxacin	primidone *	rufinamide *
lopinavir	darunavir	avasimibe	bosentan
mibefradil	diltiazem	rifabutin	efavirenz
nefazodone	elvitegravir	rifampin	etravirine
nelfinavir	erythromycin	St. John's Wort	modafenil
posaconazole	fluconazole		nafcillin
ritonavir	grapefruit juice		ritonavir
saquinavir	schisandra sphenanthera		talviraline
telithromycin	tipranavir		tipranavir
troleandomycin	tofisopam		
voriconazole	verapamil		

* These drugs are Enzyme Inducing Anti-Epileptic drugs (EIAEDs)

This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database based on in vitro studies and from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche 2008).

Appendix 2: List of CYP450 substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	adinazolam	felodipine[1]
cerivastatin	diclofenac	citalopram	alfentanil[1,2]	fentanyl[2]
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine[1]	flunitrazepam
repaglinide	fluvastatin	clomipramine	alprazolam	fluticasone[1]
rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	lovastatin[1]
torasemide	gliclazide	diazepam	aripiprazole	maraviroc[1]
troglitazone	glimepiride	fluoxetine	atorvastatin	midazolam[1]
	glipizide	imipramine	brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam[1]	nisoldipine
	irbesartan	mephobarbital	budesonide[1]	nitrendipine
	ketobemidone	moclobemide	buspirone[1]	perospirone[1]
	lornoxicam	omeprazole	capravirine	quinine
	losartan	pantoprazole	cerivastatin	sildenafil[1]
	meloxicam	progesterone	chlorpheniramine	simvastatin[1]
	naproxen	quazepam	cyclosporine[2]	sirolimus[1,2]
	nateglinide	rabeprazole	darifenacin[1]	tolvaptan
	piroxicam	sertraline	diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine[2]	triazolam[1]
	S-ibuprofen		ebastine[1]	
	sulfamethoxazole		eletriptan[1]	
	tenoxicam		eplerenone[1]	
	tolbutamide		ergotamine[2]	
	torasemide		estazolam	
	valdecoxib		everolimus[1]	

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

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

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

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

Appendix 3: Prohibited QT prolonging drugs with risk of Torsades de Pointes

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

List of prohibited QT prolonging drugs

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate

(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT
Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Note: drugs with a known risk for TdP that are also strong inhibitors of CYP3A are not repeated here and only mentioned in Appendix 2.

Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval

Appendix 4: List of QT prolonging drugs to be used with caution

Patients receiving any study treatment may use the following medications but should be monitored closely.

Drug	QT risk (*)
Alfuzosin	Possible risk for TdP
Amantadine	Possible risk for TdP
Amitriptyline	Conditional risk for TdP
Azithromycin	Possible risk for TdP
Chloral hydrate	Possible risk for TdP
Citalopram	Conditional risk for TdP
Clomipramine	Conditional risk for TdP
Clozapine	Possible risk for TdP
Desipramine	Conditional risk for TdP
Diphenhydramine	Conditional risk for TdP
Dolasetron	Possible risk for TdP
Doxepin	Conditional risk for TdP
Dronedarone	Possible risk for TdP
Escitalopram	Possible risk for TdP
Flecainide	Possible risk for TdP
Fluoxetine	Conditional risk for TdP
Foscarnet	Possible risk for TdP
Galantamine	Conditional risk for TdP
Gatifloxacin	Possible risk for TdP
Gemifloxacin	Possible risk for TdP
Granisetron	Possible risk for TdP
Imipramine	Conditional risk for TdP
Indapamide	Possible risk for TdP
Isradipine	Possible risk for TdP
Levofloxacin	Possible risk for TdP
Lithium	Possible risk for TdP
Mexiletine	Conditional risk for TdP
Moexipril/HCTZ	Possible risk for TdP
Moxifloxacin	Possible risk for TdP
Nicardipine	Possible risk for TdP
Nortriptyline	Conditional risk for TdP
Octreotide	Possible risk for TdP
Ofloxacin	Possible risk for TdP
Ondansetron	Possible risk for TdP
Oxytocin	Possible risk for TdP
Paliperidone	Possible risk for TdP
Paroxetine	Conditional risk for TdP
Perflutren lipid microspheres	Possible risk for TdP
Protriptyline	Conditional risk for TdP
Ranolazine	Possible risk for TdP
Risperidone	Possible risk for TdP
Roxithromycin*	Possible risk for TdP
Sertindole	Possible risk for TdP
Sertraline	Conditional risk for TdP

Drug	QT risk (*)
Solifenacin	Conditional risk for TdP
Tizanidine	Possible risk for TdP
Trazodone	Conditional risk for TdP
Trimethoprim-Sulfa	Conditional risk for TdP
Trimipramine	Conditional risk for TdP
Venlafaxine	Possible risk for TdP
Ziprasidone	Possible risk for TdP

Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval

Appendix 5: Patient Self-Reported Mood Questionnaires

Scoring the PHQ-9 and GAD-7

Calculating the Total Score for the PHQ-9

Total scores from the PHQ-9 will be calculated to assess depression severity according to the developer's guidelines (Instruction Manual: Instructions for Patient Health Questionnaire (PHQ) and GAD-7 Measures. Accessed on 2010 Sept 9 from: www.phqscreeners.com). This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. PHQ-9 total score for the nine items ranges from 0 to 27.

PHQ-9 Scoring Example:

In the example below, the Total Score for the PHQ-9 depression severity is 8, where the score is the sum of four items scored "0" (questions: #3, 7, 8, 9), three items scored "1" (questions: #1, 4, 6), one item scored "2" (question: #2), and one item scored "3" (question: #5).

PATIENT HEALTH QUESTIONNAIRE - 9 (PHQ - 9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

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

Calculating the Total Score for the GAD-7

Similar to the PHQ-9, scores for the GAD-7 will calculated to assess anxiety severity according to the developer's guidelines (1). This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. A total score for the GAD-7 can range from 0 to 21.

GAD-7 Scoring Example:

In the example below, the Total Score for the GAD-7 anxiety severity is 9, where the score is the sum of two items scored "0" (questions: #6, 7), two items scored "1" (questions: #2, 3), two items scored "2" (questions: #1, 5), and one item scored "3" (question: #4).

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?

(Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	☐ 0	☐ 1	☒ 2	☐ 3
2. Not being able to stop or control worrying	☐ 0	☒ 1	☐ 2	☐ 3
3. Worrying too much about different things	☐ 0	☒ 1	☐ 2	☐ 3
4. Trouble relaxing	☐ 0	☐ 1	☐ 2	☒ 3
5. Being so restless that it is hard to sit still	☐ 0	☐ 1	☒ 2	☐ 3
6. Becoming easily annoyed or irritable	☒ 0	☐ 1	☐ 2	☐ 3
7. Feeling afraid as if something awful might happen	☒ 0	☐ 1	☐ 2	☐ 3
Column totals:	*0*	*2*	*4*	*3*
GAD-7 TOTAL SCORE:			***9***	

Appendix 6: Karnofsky Performance Status Scale

SCORE	DESCRIPTION
100	Normal; no complains; no evidence of disease
90	Able to carry on normal acidity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead