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Phase II Multicenter Single-arm Study of BKM120 plus Capecitabine for Breast Cancer Patients with Brain Metastases

CBKM120ZUS39T

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Study Investigators:

Joyce O'Shaughnessy, MD
Baylor Sammons Cancer Center
3410 Worth Street
Dallas, Texas 75246
(214) 370-1796

Morris D. Groves, MD, JD
Texas Oncology
901 W. 38th St., Suite 200
Austin, TX 78705
(512) 421-4100

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List of Abbreviations

AE	Adverse Event
ADME	Absorption, Digestion, Metabolism, Excretion
AKT	See PKB (protein Kinase B)
ALT	Alanine aminotransferase/glutamic-pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartateaminotransferase/glutamic-oxaloacetic transaminase/GOT
BAL	Bronchoalveolar lavage
BC	Breast Cancer
BRCA1/2	Breast Cancer 1/2
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
C1D1	Cycle 1 Day 1
CK	Creatine Kinase
CK-MB	Creatine Kinase - Muscle and Brain isoenzyme
CNS	Central Nervous System
CR	Complete Response
CRD	Clinical Research and Development
CS	Cowden Syndrome
CT	Computed Tomography
CTI	Clinical Trial Information
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CYP3A4	Cytochrome P450 3A4
CYP450	Cytochrome P450
DLco	Diffusing capacity of the Lung for Carbon Monoxide
DLT	Dose Limiting Toxicity
Delta	Delta Clinical Research, LLC
DSMB	Drug Safety Monitoring Board
DSTPlan	Double Precision Study Planning (software)

ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Group
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EOT	End Of Treatment
ER	Estrogen Receptor
18F-FDG	[18F]-Fluorodeoxyglucose
FFPE	Formalin Fixed Paraffin Embedded
FGF	Fibroblast Growth Factor
FISH	Fluorescence In Situ Hybridization
FNA	Fine Needle Aspiration
FOXO3a	Forkhead Box O3
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GABA	Gamma-Amino Butyric Acid
GAD-7	Generalized Anxiety Disorder Scale 7
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GPA	Graded Prognostic Assessment
GSK3 beta	Glycogen Synthase Kinase-3
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
hERG	Human Ether-à-go-go Related Gene
HIAA	5-Hydroxyindoleacetic Acid
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HPF	High Power Field

ICH	International Conference on Harmonization
IC50	Half-maximal Inhibitory Concentration
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
IHC	Immunohistochemistry
INPP4B	Inositol Polyphosphate 4-phosphatase type II
INR	International Normalized Ratio
IRB	Institutional Review Board
LDL	Low density lipoprotein
LFT	Liver Function Test
LFU	Lost to Follow Up
LumA	Luminal A
LumB	Luminal B
LVEF	Left Ventricular Ejection fraction
MBC	Metastatic Breast Cancer
MDASI-BT	M.D. Anderson Symptom Inventory – Brain Tumor
MEFs	Mouse Embryonic Fibroblasts
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MTOR	Mammalian Target of Rapamycin
MTORC2	mTOR Complex 2
NE	Non-evaluable
NEC	Not Elsewhere Classified
MUGA	Multiple Gated Acquisition Scan
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PD	Pharmacodynamic
PDFG	Platelet Derived Growth Factor
PET	Positron Emission Tomography
PgR	Progesterone Receptor
PHQ9	Patient Health Questionnaire 9
PI3K	Phosphatidylinositol 3’-kinase

PIP3	Phosphatidylinositol Phosphate 3
PK	Pharmacokinetic
PKB	Protein Kinase B (or AKT)
PR	Partial Response
pS6	Phosphorylated S6 Protein of the 40S Ribosomal Subunit
PT	Prothrombin Time
PTEN	Phosphatase and Tensin homolog
PTT	Partial Thromboplastin Time (also known as APTT)
QTc	QT interval (corrected)
RAD001	Everolimus
RAS1	Rat Sarcoma Gene 1
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
S6K	Protein Kinase S6
SAE	Serious adverse event
SD	Stable Disease
SHIP2	SH2-containing 5'-Inositol Phosphatase 2
SI	Study Investigator
SOP	Standard Operating Procedure
Src	Src Nonreceptor Tyrosine Kinase
SRS	Stereotactic Radiosurgery
SUV	Standardized Uptake Value
TCGA	The Cancer Genome Atlas
TdP	Torsades de Pointes
TNBC	Triple Negative Breast Cancer
TR-FRET	Time Resolved-Fluorescence Resonance Energy Transfer
TSC1	Tuberous Sclerosis Complex 1
TTP	Time to Progression
ULN	Upper Limit of Normal
UPN	Unique Patient Number
VPs34	Class III Phosphoinositide 3-Kinase Isoform
WBC	White Blood Count

WBRT	Whole Brain Radiation Therapy
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

Synopsis

This is a Phase 2, multicenter, single-arm study to determine the safety and efficacy of buparlisib (BKM120) plus capecitabine in breast cancer patients with brain metastases. 42 patients will be included, who have either ER+/HER2-, HER2+ or triple negative breast cancer.

The primary objective will be to determine the clinical benefit rate (CBR) defined as the proportion of patients with the best overall response of complete response (CR) or of partial response (PR) or of stable disease (SD) lasting at least 24 weeks. The Graded Prognostic Assessment (GPA) is a recently developed, validated prognostic score for patients with brain metastases (Sperduto 2008, Sperduto 2012b). The Graded Prognostic Assessment will be utilized to evaluate efficacy in this clinical study. Secondary objectives include an assessment of objective response rate (ORR) in the CNS, the median time to progression (TTP) and the median overall survival (OS) as well as the usual requirement to characterize the safety and tolerability of the combined buparlisib plus capecitabine therapy.

Capecitabine is a prodrug which is enzymatically converted to 5-fluorourocil in its tumor target where it inhibits DNA synthesis and slows tumor growth. It is currently FDA approved for both colorectal and breast cancer. Buparlisib is a pan phosphatidylinositol-3-kinase inhibitor being developed under IND# 102,823 by Novartis Corporation. As of September 2012 over 600 patients had been enrolled in fourteen separate Novartis sponsored monotherapy or combination therapy clinical studies of buparlisib which are summarized in Section 1.3.1.3.1.

Phosphatdyinositol-3-kinase (PI3K) signaling regulates diverse cellular functions including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso, et. al., 2001). PI3K signaling also serves a central role in the pathogenesis of numerous cancers. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including hormonal therapyanti-HER2 therapies and chemotherapy can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006).

Preliminary data suggest that activation of the PI3K pathway is a predictor of a poor prognostic outcome in many cancer types. Thus, as a pan-PI3K inhibitor, buparlisib may provide a therapeutic benefit to patients with MBC. Both capecitabine and buparlisib have previously shown activity in patients with MBC. Like capecitabine, buparlisib is also effective in crossing the blood brain barrier making it a preferred candidate for its evaluation in patients with MBC.

Current clinical experience with buparlisib has shown that its most frequent adverse events (AEs) include fatigue, decreased appetite, diarrhea, hyperglycemia, nausea, rash and mood alteration disorders. Therefore patients will be closely monitored for fasting plasma glucose (FPG) HbA1c, and insulin C-peptide. Patients will also be frequently and routinely evaluated for mood disorders and disturbances. The remaining most frequent AEs will be detected by regular, frequent monitoring with symptomatic treatment to be provided as required.

1 Background

1.1 Disease Background

Breast cancer (BC) is the most common form of malignant tumor in women worldwide, and incidence rates are as high as 99.4 per 100,000 women (World Health Organization 2011). Subtypes of BC are distinguished by expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor-2 (HER2), as well as by distinct gene expression profiles (Perou 2000; Sotiriou and Pusztai 2009).

Patients with metastatic ER-negative breast cancer have a high risk of developing brain metastases. In one retrospective cohort study, 46% of patients with metastatic triple negative breast cancer (TNBC) were found to have central nervous system (CNS) metastases at some point before death, and 14% had a CNS metastasis at first metastatic presentation (Lin 2008). A second retrospective study reported a 25% incidence of CNS metastases in patients with TNBC (Kennecke 2010). Outside of surgery and radiation therapy there are no proven therapies which improve overall survival (OS) of patients with brain metastases. In patients with HER2+ MBC, retrospective studies have documented an incidence of CNS metastases of approximately 25% - 40%, and this frequently occurs while systemic disease is still well controlled by effective HER2-targeted therapies (Lin 2007). A study of breast cancer patients in the British Columbia Cancer Agency reported a 15 year incidence rate of CNS metastases of 5% and 2% in estrogen receptor-positive Luminal B and Luminal A subtypes, respectively (Kennecke 2010). However, patients with ER+ breast cancer brain metastases are more prevalent than patients with TNBC or HER2+ brain metastases because the majority of metastatic disease is ER+ HER2-negative (Sperduto 2012)

The American Society of Therapeutic Radiation Oncology (ASTRO)'s guidelines regarding radiation therapy for breast cancer brain metastases have changed, in recent years now de-emphasizing the role of whole brain radiation (WBRT) and expanding the role of stereotactic radiosurgery (SRS) (Tsao M, et al.,2012)

In this new guideline, any number of brain metastases are appropriate for SRS provided they are not over 3cm in size and provided they can be treated in one radiation therapy session. WBRT is administered only for the development of new metastases following SRS, and only if there are more than 3 new metastases. If 1-3 new metastases following previous SRS, repeated SRS is preferred and WBRT is reserved for patients with more than 3 new metastases following WBRT. ASTRO has emphasized SRS over WBRT because of the considerable toxicity of WBRT and the lack of improved survival or other clinical outcomes with WBRT compared with SRS.

Most systemic therapies are ineffective due to the impenetrability of the blood/brain barrier, the intrinsic resistance of CNS metastases, and expression of the P-glycoprotein efflux pump. In the published natural history studies, the median OS time for patients with triple negative (TN) brain metastases is approximately 4 months (Lin 2008; Anders 2007; Adamo 2007, Nam 2008; Eichler 2008). Another retrospective study of outcomes in patients with breast cancer-associated CNS metastases by subtype reported mean OS times of 61.2 and 39.0 months for luminal A and luminal B estrogen receptor-positive cancers, respectively, and a mean OS of 20.3 months for

HER2+ cancers (Wiens 2014). The Sperduto Graded Prognostic Assessment Tool further refines OS estimates based on age and performance status. ER+ brain metastases in woman with symptoms and/or over age 60 is associated with OS rates less than 2 years (Sperduto 2008 and Appendix 1).

The Graded Prognostic Assessment (GPA) is a recently developed, validated prognostic score for patients with brain metastases (Sperduto 2008). The GPA has been further refined and updated to create diagnosis-specific indices, including a breast cancer-specific GPA (Sperduto 2012a; Sperduto 2012b; Barnholtz-Sloan 2012). GPA scores range from 4.0 (best prognosis) to 0.0 (worst prognosis), based on weighted significant prognostic factors, and can be used to estimate survival for individual patients. The components for the breast cancer GPA are tumor subtype, Karnofsky performance score, and age. A recent study that utilized the GPA showed that patients with TNBC and brain metastases had a median survival time of 6.4 months (Sperduto 2012b).

Brain metastases in patients with TNBC are life-limiting metastases. Therapies which change the natural history of this condition are urgently needed.

1.2 PI3K Pathway and Mechanism of Action

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

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

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

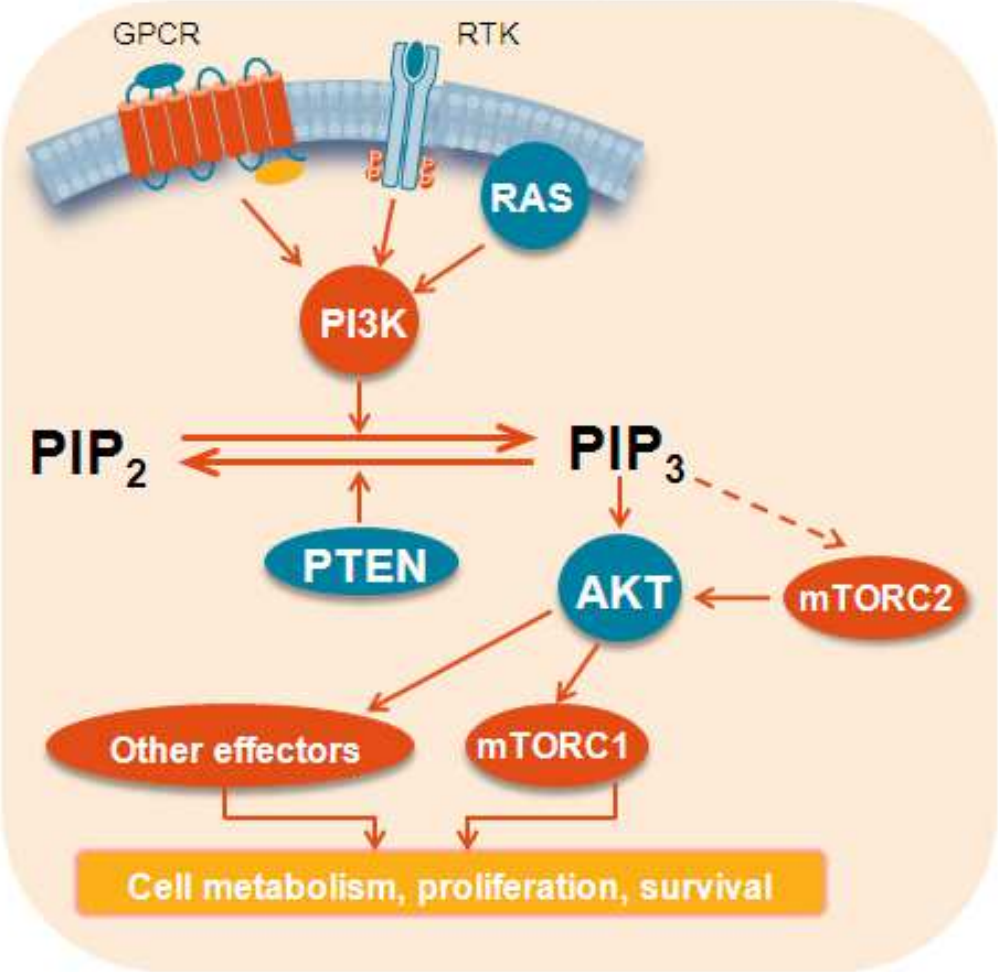
a. Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins) or
b. Loss-of-function mutations or epigenetic alterations affecting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

Together, these observations suggest that PI3K pathway could be a critical therapeutic target for the treatment of patients with advanced solid malignancies who often have limited therapeutic

options beyond institutional standard of care. Hence, treatment with the pan-PI3K inhibitor buparlisib (BKM120) potentially addresses an unmet medical need in such patients.

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

Figure 1-1 Schematic representation of the PI3K pathway



1.2.1 PI3K pathway activation in MBC

The PI3K pathway can be alternatively activated through various receptor classes or cross-talk with other pathways. In TNBC, the PI3K pathway appears to be modulated by the EGFR. Preclinical models have demonstrated that EGFR signaling through the PI3K pathway leads to a higher level of Akt phosphorylation in TNBC cell lines (Umemura 2007; Marty 2008; reviewed by Moulder 2010). Interestingly, TNBC cell lines have also been associated with lower expression of PTEN, which correlates with increased activation of Akt and portends a favorable response to PI3K inhibition. Indeed, cell lines which are wild type for PIK3CA, but have lost PTEN expression can be sensitive to a PI3K inhibitor (O'Brien 2010). These agents, therefore, present an intriguing class of targeted anti-cancer therapy for patients with TNBC. The epidemiology data reported so far present significant variation (Stemke-Hale 2008; Humphrey

Gardner unpublished; Lopez-Knowles 2010; Hernandez-Aya and Gonzalez-Angulo 2011) (Table 1.1), however, based on these numbers, approximately 48% of triple negative breast cancers should be PI3K pathway activated (either *PIK3CA* mutated or PTEN loss).

Up to 40% of HR+/HER2- cancers also exhibit activation of PI3K pathway, via PIK3CA mutation or PTEN loss (Stemke-Hale 2008; Humphrey Gardner unpublished; Lopez-Knowles 2010; Hernandez-Aya and Gonzalez-Angulo 2011). Bidirectional crosstalk between the ER/PR and PI3K pathways has been shown to influence ER/PR levels and activity, including phosphorylation and genomic activation of the ER, while membrane ER signaling can activate PI3K/Akt (Hernandez-Aya and Gonzalez-Angulo 2011). Experimentally, PI3K pathway activation has been associated with de novo and acquired resistance to endocrine therapy (Campbell 2001) including AI resistance (Shoman 2005; Crowder, 2009; Miller, 2011).

A substantial fraction of HER2-amplified breast cancers also demonstrate activation of the PI3K pathway, primarily through loss of PTEN (Table 1-1). Activation of this pathway, either by PIK3CA mutation or PTEN loss, has been associated with resistance to trastuzumab, and cell line research suggests that inhibition of the PI3K pathway is an important mechanism of action for trastuzumab (Hernandez-Aya and Gonzalez-Angulo 2011). Further, synergistic activity has been observed with combinations of trastuzumab and PI3K inhibitors in breast cancer cell line studies (Hernandez-Aya and Gonzalez-Angulo 2011).

Genomic and phosphoproteomic analysis of human primary breast cancers in the TCGA showed strong activation of PI3K pathway signaling in the majority of basal breast cancers, as well as PIK3CA mutations in 45% of Luminal A cancers, 29% of luminal B cancers, and 39% of HER2-enriched cancers (Cancer Genome Atlas Network 2012).

Table 1-1 PI3K signaling pathway mutations and alterations in breast cancer [1; 2; 3; 4]

	Mutation		**Alteration**
	PIK3CA	***PTEN* Mutation [1]**	**PTEN loss of expression**
All Breast Tumors	10-40%	~2%	29-50%
HR(+) HER2(-)	7-40%	2-4%	19-29%
Triple Negative	6-9%	0%	15-66%
HER2-amplified	20-25%	-	30-40%

([1] Stemke-Hale 2008, [2] Humphrey Gardner, Oncology Translational Laboratories, Novartis, unpublished [3] Lopez-Knowles 2010 [4] Hernandez-Aya and Gonzalez-Angulo, 2011. Ranges represent the minimum and maximum incidence reported in these trials. Trial incidence calculations were made using the midpoint of the range.

A study of the PI3K pathway specifically in breast cancer brain metastases found activation of this pathway in the majority of cases, regardless of breast cancer subtype, although PTEN loss was most common in the TNBC subtype (37%, vs 17% in HR_/HER2- and 25% in HER2+) (Adamo 2011).

In addition to mutation of *PIK3CA*, and loss or mutation of *PTEN*, loss of the tumor suppressor *INPP4B* (inositol polyphosphate 4-phosphatase-II) is emerging as an important activator of PI3K signaling in triple-negative or basal-like breast cancers. Preclinical studies in breast cancer cell lines showed that inactivation of INPP4B leads to Akt activation, cell proliferation, and growth of tumor xenografts (Fedele 2010). Investigation of INPP4B protein expression in primary breast cancers found loss of expression most frequently in basal-like primary breast cancers (84%); INPP4B loss was also associated with high clinical grade and tumor size (Fedele 2010). The Cancer Genome Atlas study, which used a variety of genomic and proteomic methods of analysis, found that *PIK3CA* mutations occurred in 7% of basal-like breast cancer, *PTEN* mutation or loss occurred in 35%, and loss of *INPP4B* occurred in 30% (Cancer Genome Atlas Network). In another study, DNA copy number aberration analysis combined with breast cancer intrinsic subtyping found loss of *INPP4B* in 40% - 47.5% of basal-like breast cancers, and loss of *PTEN* in 22.5% - 34%, using two different datasets containing 40 and 61 patient samples, respectively (Weigman 2012). Finally, a recent study that used whole genome and transcriptome sequencing to analyze 14 metastatic TNBCs revealed that the PI3K/Akt/mTOR pathway was activated due to genomic changes in 5 cases, most frequently through loss of *PTEN* or *INPP4B*, as well as at the transcription level with decreased INPP4B or PTEN mRNA levels in nearly all patients (Craig 2013).

Another pathway that has been associated with metastatic colonization of the central nervous system (CNS) in breast cancer is the HER3/neuregulin 1 axis which strongly activates the PI3K pathway. Neuregulin 1 (heregulin), a ligand for HER3, is abundant in brain tissue, and one study reported overexpression and activation of HER3 in brain metastases compared with matched primary breast cancer samples (Da Silva 2010). Within the HER family of receptors, activation of PI3K signaling is driven primarily through transphosphorylation of the kinase-inactive HER3 receptor, which has also been implicated in resistance to HER2-targeted therapies in HER2+ breast cancers (Hsieh 2007). HER3 expression has also been associated with a poorer prognosis in both TNBC and HER2+ breast cancers (Bae 2013). In addition, signaling through HER3 has been implicated in resistance to the estrogen receptor downregulator fulvestrant in an ER+ breast cancer xenograft model system (Osipo 2007).

These studies suggest that through a variety of mechanisms, activation of the PI3K signaling pathway is likely to occur in the vast majority of metastatic breast cancers, and thus rendering PI3K a promising therapeutic target.

1.3 Study Treatments

1.3.1 Buparlisib

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

1.3.1.1 Preclinical studies

Buparlisib activity against class I PI3K (p110α, -β, -δ and -γ), Class III (Vps34), the class IV mTOR related PI3K or PI4Kβ, was assessed using either a luciferase luminescence (class I or III PI3Ks and PI4Kβ) or a TR-FRET assay (Class IV mTOR). The IC50 in these assays is outlined below in Table 1.2.

Table 1.2 Inhibitory activities (IC50) of buparlisib against other PI3K or related kinases

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

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

Buparlisib significantly inhibits p110α and the most common p110α mutations (H1047R, E454K, E542K), p110β, p110δ and p110γ. Buparlisib is classified as a pure pan-class I PI3K inhibitor. Enzymatic characterization of the inhibitory properties of the compound revealed that buparlisib is a mixed inhibitor of PI3Kα with a strong competitive component (largest for Vmax). The cocrystal X-ray structure of buparlisib with PI3Kγ confirmed that buparlisib interacts with PI3K into the ATP catalytic cleft. As shown in Table 1.3, buparlisib is also selective (50-fold difference) toward p110α compared to other protein kinases.

Table 1.3 Activity of buparlisib in the Novartis kinase panel

Kinase	Type	IC_{50}
Axl	RTK	>10
Fak	Cytosolic TK	>10
Kdr	RTK	>10
PKA	Cytosolic Ser / Thr Kin.	>10
PKB	Cytosolic Ser / Thr Kin.	>10
Ret	RTK	>10
Tek	RTK	>10
CDK2/cyclinA	Cytosolic Ser / Thr Kin.	>10
PDK1	Cytosolic Ser / Thr Kin.	>10
B-Raf V599E	Cytosolic Ser / Thr Kin.	9.2
HER-1	RTK	>10
c-Abl	Cytosolic TK	>10
c-Abl- T315I	Cytosolic TK	>10
c-Met	RTK	>10
c-Src	Cytosolic TK	>10
IGF1-R	RTK	>10
Eph-B4	RTK	>10
Jak2	Cytosolic TK	>10
FGFR3-K650E	RTK	>10
All IC_{50}'s are expressed in µM		

Activity in mechanistically driven cell-based models

The PI3K pathway regulates the activity of the mTORC1 complex, when cells are challenged through mitogenic stimuli. In order to assess in cells the potential impact of the buparlisib on the mTORC1 complex, the compound was tested in TSC1 null cells. These cells express a constitutively activated mTORC1 complex that uncouples the mTOR pathway from the PI3K upstream input (Kwiatkowski 2003). When exposed to TSC1 null MEFS, buparlisib reduced the S235/236P-RPS6 levels with an IC50 of 1785 nM, in agreement with the data obtained in the mTOR biochemical assay. In contrast, and as expected the allosteric mTORC1 inhibitor RAD001 displayed sub-nanomolar inhibitory activity in this assay.

PI3K pathway inhibition potency and specificity in relevant cell-based disease models

In contrast to molecules with a distinct mechanism of action (e.g., the BCR-Abl inhibitor STI571, mTORC1 allosteric inhibitor RAD001), buparlisib is able to decrease the phosphorylation status of various either direct (GSK3β, FKHRL1/FOXO3a) or indirect downstream Akt effectors (p70S6K, through mTOR) in the PTEN null U87MG cell line, as efficiently as prototypical PI3K inhibitors such as LY294002 and Wortmannin.

In all cases, buparlisib showed specific PI3K pathway attenuation as demonstrated by specific attenuation of S473P-Akt levels without affecting the non-PI3K-driven read–outs such as activated receptors (EGFR, PDGFR), MAP kinases (ERK, JNK and p38) or Jak cytosolic tyrosine kinases responsible for Stat transcription factor phosphorylation.

1.3.1.2 Preclinical Safety

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

1.3.1.2.1 Pharmacodynamics

Buparlisib inhibits wild-type PI3Kα (IC_{50}: 35 nM), with at least 50-fold selectivity towards this compared to activity against other protein kinases outside the PI3K family. The compound is equipotent against somatic PI3Kα mutants (H1047R-, E542K-, and E545K-p110α), and is active against the other three PI3K paralogs (PI3Kβ, -γ, -δ; IC50 108 to 348 nM range). Buparlisib does not significantly inhibit the related kinases mTOR or Vps34, nor does it inhibit (IC_{50} >10 μM) other receptors and ion channels profiled.

Buparlisib reduces the phosphorylation of the direct downstream effector Akt in relevant tumor cell lines (e.g., IC_{50} 93 nM for S473P-Akt in Rat1-p110α cells). This biological activity correlates with inhibition of various other downstream signaling components and with antiproliferative activity in a variety of tumor cell lines.

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

Antitumor activity of buparlisib in breast cancer

Preclinical data in models of breast cancer are emerging that support buparlisib evaluation in clinical studies. In a series of 20 basal breast cancer cell lines, 4 lines carrying a loss of a phosphatase related to PTEN, INPP4B, displayed sensitivity to buparlisib (between 17 and 30% cell death) (Gerwinner 2009). The sensitivity to buparlisib has been confirmed in xenograft models where stasis and regressions have been observed in models mostly driven by loss of PTEN. Treatment of TNBC cell lines and patient-derived TNBC xenografts with buparlisib has also been shown to increase DNA damage, downregulate BRCA1/2, and increase poly-ADP-ribosylation (Ibrahim 2012). Likewise, in a BRCA1-related breast cancer mouse model, buparlisib delayed tumor doubling time, and reduced AKT phosphorylation, tumor proliferation, and angiogenesis (Juvekar 2012).

Preclinical in vitro and in vivo models suggest that buparlisib has an inhibitory effect in breast cancer models (Maira et al 2012).. In a panel of 44 cell lines, buparlisib induced cell death in the majority of luminal breast cancer lines (12/18) as well as 4/20 basal-type cell lines. This was confirmed in xenograft models, where HER2+ and ER+ models displayed tumor control for up to 120 days (O'Brien et al 2011), and triple-negative primary tumor models displayed stasis or occasional regression.

Furthermore, AI resistance has been associated with activation of PI3K pathway (Crowder 2009, Miller 2011) and *in vitro* response to buparlisib was also observed in ER-positives cell lines before and after long-term estrogen deprivation (Sanchez 2011). These cell lines included various mechanisms of PI3K pathway activation (i.e., PIK3CA mutation, HER2 amplification, or PTEN mutation.

Finally, buparlisib was also shown to be efficacious in controlling brain metastasis in a preclinical model of human $HER2^+$ breast cancer in $Rag2^{-/-}$;$Il2rg^{-/-}$ mice (Nanni 2012).

This activity of buparlisib observed in pre-clinical models provides strong molecular evidence for the role of PI3K signaling in MBC and supports the exploration of buparlisib in this disease setting.

1.3.1.2.2 Nonclinical pharmacokinetics and metabolism

Buparlisib showed favorable pharmacokinetic properties in all animal species tested. The absorption of [^{14}C]-buparlisib -related radioactivity was >84% in the rat. Oral bioavailability was moderate to high in rats, dogs, monkeys (42-100%). The estimated steady state plasma volume of distribution (Vss) was moderate in all species (3.0-3.5 L/kg). Buparlisib penetrates the blood brain barrier in rats with a tissue-to-plasma ratio about 2. Buparlisib is moderately bound to plasma protein across all species examined (free fraction ~15% and independent of concentration in humans).

Oxidative metabolism of buparlisib is predominantly mediated by CYP3A4 (estimated fraction metabolized >0.9). Direct phase II metabolism (glucuronidation) via UGT1A4 is also observed in human liver microsomes supplemented with UDPGA. All phase I metabolites identified in human hepatocytes and microsomes were also detected in animals. Buparlisib and identified metabolites have a low potential for covalent binding to protein.

Buparlisib is weak reversible inhibitor of CYP3A4 (Ki = 13.6 µM) and it also weakly inhibits the CYP2C family (2C8, 2C9 and 2C19) with IC50 values ranging from 35 –65 µM. Buparlisib does not show time-dependent inhibition of CYP450 enzymes. With respect to transporter-based drug-drug interactions, buparlisib is neither a substrate for MRP-2, OATP1A2, OATP1B1, OATP1B3, OATP2B1, P-gp nor an inhibitor for BCRP, MATE1, MATE2K, MRP2, OAT1, OAT3, OCT2, P-gp in the observed range of clinically relevant concentrations. It is possible that buparlisib activates the pregnane X receptor (PXR) in vivo and induces CYP3A4 at concentrations ≥50 µM, however, the absence of any time dependent changes in the pharmacokinetics of buparlisib in the relevant therapeutic dose range in humans, suggests that this may not be relevant in vivo. Finally, experiments showed a potential for buparlisib to induce UGT1A1 at concentrations between 0.5 and 100 µM. The mean maximum free concentration calculated at steady state for the 100 mg qd dose in the study [CBKM120X2101] was 0.671 µM (Cmax,tot=4.20 µM). Therefore a potential induction of UGT1A1 cannot be formally excluded however the clinical relevance of observed activation of UGT1A1 activity is unclear.

In GLP toxicology studies, buparlisib exposure in terms of AUC0-24h and Cmax increased in a dose proportional manner in rat and dog. There was no noticeable drug accumulation in dog or

male rats after 13 weeks of daily dosing. There was a slight accumulation in female rats (<2 fold).

1.3.1.2.3 Safety pharmacology and toxicology

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. When using a microdialysis technique to investigate the effect of a single or 2-week repeated dosing of buparlisib in various brain regions of rats, a marked increase in extracellular levels of gamma-aminobutyric acid (GABA) were observed in the ventral hippocampus (vHPC) and median prefrontal cortex (mPFC), both under acute as well as repeated dosing conditions. In the same brain regions, smaller increases in levels of dopamine, serotonine and noradrenaline were observed in the vHPC, with a trend to decreased corticosterone. Cardiac safety studies, conducted *in vitro* and *in vivo* did not indicate a prominent electrophysiological risk. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, which was observed in two dog telemetry studies, in the absence of an electrophysiological effect.

Repeated-dose studies (up to 13 weeks of duration) were performed in rats and dogs. In rats, clinical pathology and histopathology findings showed a decrease in lymphocyte counts in the peripheral blood, decreases in germinal center development in different lymph nodes, and lymphocytolysis in the thymus. In dogs, similar findings were made. In both species, erythropoiesis was affected, as evidenced by reduced erythrocyte counts accompanied by bone marrow suppression observed in rats.

The pancreas was affected by treatment with buparlisib, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. At higher doses in the 2-week dose-range-finding study in rats, there were histopathological findings in both the endocrine and in the exocrine pancreas.

Male reproductive organs and associated tissues were found to be targets of toxicity in both rats and dogs. Changes included minimal to slight germ cell depletion, formation of spermatic giant cells and abnormal spermatids, plus cellular debris in epididymal tubules. Testicular toxicity did not fully reverse after the 4-week treatment-free period in rats, although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles. In dogs, there was no effect on female reproductive organs.

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

Buparlisib does not have sensitizing or irritative potential in the skin.

No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro with buparlisib. However, a potential for genotoxicity was identified based on the observation of an aneugenic potential and was confirmed by fluo rescence in situ hybridization of centromeric sequences within micronuclei induced in human peripheral lymphocytes in vitro. In line with this result, buparlisib treatment resulted in an elevated frequency of micronucleated polychromatic erythrocytes in the bone marrow of rats. In

summary, evidence of a genotoxic potential with buparlisib has been seen in vitro and in vivo and is likely due to an aneugenic effect.

In a rat embryofetal dose-range finding study, buparlisib treatment induced embryolethality and implantation loss, together with foetal pathology changes at doses that were only minimally maternally toxic. No phototoxic potential or any effect on wound healing has been identified with buparlisib in pre-clinical studies.

In summary, the toxicity and safety pharmacology profile of buparlisib can be associated primarily to the expected pharmacodynamics activity of buparlisib. Main target organs for toxic effects were the hematopoietic and lymphopoietic systems and the reproductive tract. Buparlisib is genotoxic via an aneugenic mechanism, and it interferes with insulin signaling and the associated metabolic disturbances. The compound may have an influence on central neurotransmitter levels, but this effect needs to be further evaluated. Overall, these findings are compatible with the treatment of advanced cancer and do not preclude the use in the foreseen indications.

1.3.1.2.4 Pharmacodynamic biomarkers

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

1.3.1.3 Clinical experience

1.3.1.3.1 Clinical experience with buparlisib

As of 15 September 2013, approximately1469 patients and healthy volunteers have been enrolled into twenty-two clinical studies with buparlisib (as single agent or in combinations). The Novartis sponsored clinical studies were:

- Phase I single agent studies [CBKM120X2101], [CBKM120X1101], and [CBKM120Z2102], [CBKM120C2110], [CBKM120C2104], [CBKM120C2106], [CBKM120C2111], and [CBKM120C2102].
- Phase II single agent studies [CBKM120C2201] and [CBKM120D2201]
- Phase I combination studies [CBKM120B2101], [CBKM120X2107], [BKM120E2101], [CBEZ235A2118], [LDE225X2114], [CSTI571X2101], [CMEK162X2101], [CMEK162X2101], [CINC424A2104], and [CBEZ235D2101.
- Phase II combination study [CBKM120F2202]
- Phase III combination studies [CBKM120F2302] and [CBKM120F2303].

With regard to the current protocol, results presented below will focus on phase I single agent studies ([CBKM120X2101], [CBKM120X1101]), and phase I combinations in breast cancer

patients ([CBKM120X2107], [CBEZ235A2118]). Please refer to the current version of the IB for more detailed information.

1.3.1.3.1.1 Human safety and tolerability data

Recruitment in study [CBKM120X2101] has been completed with forty (40) patients included in the dose escalation phase at 6 dose levels (all once daily) (12.5 mg (1 patient); 25 mg (2), 50 mg (5), 80 mg (11), 100 mg (17), 150 mg (4)). Dose limiting toxicities were hyperglycemia, skin rash, epigastric pain, mood disorder and joint pain. The MTD for buparlisib given as single agent, once daily was established at 100 mg/day (Bendell, 2012). Forty-three additional patients were treated in the expansion cohort at 100 mg/day. At the cut-off date of July 4th 2011 (Graña 2011), patient characteristics for the 82 patients analyzed were as follows: median age 55 years (range 30–78); ECOG performance status 0/1/2 for 35/46/1 patients, respectively. The safety experience for this single agent trial of buparlisib is described in Table 1-3:

Table 1-3 Most frequent AEs (≥ 15%) related to study drug study CBKM120X2101 (n=81):

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

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

The safety and efficacy of buparlisib combined with trastuzumab in patients with relapsing HER2-overexpressing BC who have previously failed trastuzumab are being explored in a phase Ib/II, multi-center study [CBKM120X2107]. The combination of buparlisib and trastuzumab was shown to be tolerable, and with one dose-limiting toxicity (G3 asthenia) the MTD for buparlisib was declared at 100 mg/day (Saura 2011). Among the 18 patients evaluated in the PhIb part, the following G3/G4 AEs were observed: asthenia, ALT elevation, hyperglycemia, mood alteration, affective disorder, hypersensitivity, photosensitivity reaction, and rash. These AEs were all short-lived and reversible with either dose interruption or modifications as needed. In the phase

II portion of the study, as of June 2012, 53 patients have been enrolled and received buparlisib at the recommended phase 2 dose (RP2D) of 100 mg/day in combination with trastuzumab (Pistilli ESMO 2012). Overall the treatment was well tolerated. Most common AEs (>15%) included gastro-intestinal toxicity (e.g. diarrhea, nausea, stomatitis), rash, fatigue, transaminase increase, hyperglycemia, depression and anorexia. No G4 AEs have been reported. Most common G3 treatment related AEs included transaminase increase (~10%), rash (9%) and fatigue (6%), and were consistent with phase Ib findings with as well as single agent buparlisib.

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

Liver Toxicity

Liver toxicity has been analyzed based on a search of multiple MedDRA event terms (SMQ pertinent to hepatobiliary toxicity), and is presented in Table 1.5 Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly reversible transaminase increases (ALT and/or AST), and have been rarely associated with signs or symptoms of impaired liver function. The increase in AST/ALT values typically occurred within the first 6 to 8 weeks of study treatment.

The highest rates of transaminase increase have been observed on the Phase I Japanese and Chinese studies [CBKM120X1101] and [CBKM120Z2102] as well as in combination with fulvestrant in the randomized Phase 3 study [CBKM120F2302]. In contrast, the rate of transaminitis appeared to be lower in combination studies with taxanes (e.g. studies [CBKM120D2205], [CBKM120F2202] and [CBKM120H2201]) in which also steroids have been administered regularly as part of the standard premedication. In addition, transaminitis was infrequent in the lymphoma study [CBKM120Z2402].

Table 1.5 Number (%) of patients with liver toxicity regardless of study treatment relationship, occurred at 100 mg / day in BKM120 studies - Safety Set

Study Number (n= number of patients treated with 100 mg/d BKM120)	All grades n (%)	Grade 3/4 n (%)
Single agent studies		
CBKM120X2101 (n=55)	22 (40.0)	16 (29.1)
CBKM120X1101 (n=9)	4 (44.4)	4 (44.4)
CBKM120C2201 (n=70)	29 (41.4)	19 (27.1)
CBKM120D2201 (n=63)	20 (31.7)	8 (12.7)
CBKM120Z2102 (n=17)	11 (64.7)	4 (23.5)
CBKM120Z2402 (n=26) DLBCL	2 (7.7)	0 (0.0)
CBKM120Z2402 (n=22) MCL	3 (13.6)	1 (4.5)
CBKM120Z2402 (n=24) FL	1 (4.2)	0 (0.0)
Combination studies		
CBKM120X2107 (phase II n=53)*	23 (43.4)	13 (24.5)
CBEZ235A2118 (n=35)**	6 (17.1)	2 (5.7)
CBEZ235A2118 (n=11)***	2 (18.2)	1 (9.1)
CBKM120B2101 (n=34)****	14 (41.2)	5 (14.7)
CBEZ235D2101 (n=20)	1 (5.0)	0 (0.0)
CBKM120D2205 (n=11)*****	1 (9.1)	1 (9.1)
CBKM120E2102 (n=14)******	0	0
CBKM120F2202 (n=202)**	51 (25.2)	17 (8.4)

Study Number (n= number of patients treated with 100 mg/d BKM120)	All grades n (%)	Grade 3/4 n (%)
CBKM120F2302 (n=573)*******	317 (55.3)	206 (36.0)
CBKM120H2201 (n=76) **	14 (18.4)	5 (6.6)

* This number includes 3 patients who were treated with trastuzumab but did not receive treatment with BKM120.
** Combination BKM/ 80 mg Ptx
*** Combination BKM/Ptx/Tz
**** Data corresponding to MTD defined to be 70mg QD (in this study no patient was treated with BKM120 at 100mg).
***** Combination with docetaxel at 75 mg/m2
****** Combination with carboplatin AUC5
******* Combination with fulvestrant 500mg every 28 days cycle

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

A search and review of potential drug-induced liver injury (DILI) cases in Novartis-sponsored trials with buparlisib using conservative biochemical criteria (e.g. AST/ALT >3.0x ULN and TBL>2.0xULN) has shown that most of these cases occurred in the context of disease progression in advanced cancer patients and/or were confounded by other causes. However, for some of the DILI candidates causal relationship with study treatment cannot be ruled out. An aggregated safety findings report (ASFR) has been sent to all investigators/health authorities participating in buparlisib trials in May 2015 informing them about the liver toxicity findings.

As of 08-Sep 2015, in total 8 DILI cases consistent with Hy's Law have been identified upon medical review across the buparlisib program. Six out of these cases occurred in combination with fulvestrant, one in combination with letrozole and one in combination with LDE225. All patients have recovered upon treatment discontinuation except one patient for whom the outcome is not available because the patient refused to return for safety follow-up. A summary of the 8 cases is provided in below Table 1.6 Thus far, no fatal cases have been reported in the context of DILI.

Table 1.6 DILI cases consistent with Hy's Law, as of 08-Sep-2015

Study/ Subject number	Summary
CBKM120F2302 - patient 5018001 (fulvestrant + 100 mg/d buparlisib)	59 year-old female patient with breast cancer and no pre-study history of hepato-biliary conditions disorders. At study baseline, the patient had no known metastases in the liver. Under study medication the patient developed 34 fold increase of ALT and AST, 16 fold increase in total bilirubin and 2 fold increase in ALP. The patient was asymptomatic. Study treatment with BKM120 was permanently discontinued due to elevated liver function tests. The patient fully recovered. The investigator reported that the event was suspected to treatment with BKM120 and not suspected to fulvestrant
CBKM120F2302 – patient 2302002 (fulvestrant + 100 mg/d buparlisib)	60 year-old female patient with metastatic breast cancer (bone metastasis), history of depression, osteoporosis, headaches, dyspnea, back-pain and elevated AST/ALP (Grade 1) and GGT (Grade 2) at baseline. On Day 43, the patient developed Grade 3 transaminitis which worsened to Grade 4 on Day 48; treatment with buparlisib/placebo was permanently discontinued due to this event. Bilirubin was increased to Grade 2 from Day 48 to 50. The patient received ciprofloxacin for infection (from Day 48 to 52), dexamethasone for transaminitis (from Day 50 to 63) and spironolactone for abdominal distention/ ascites (from Day 48 to 53). She further took 3 herbal preparations during 1 week prior to the event, and received zoledronic acid medication for bone metastasis. The patient recovered from the event.
CBKM120F2302 – patient 2700014 (fulvestrant +100 mg/d buparlisib)	65 year-old-female patient with metastatic breast cancer (liver and bone metastasis), history of rheumatoid arthritis and elevated AST (Grade 1) at baseline. On Day 42 she developed Grade 1 transaminitis which worsened to Grade 4 on Day 64; study treatment was permanently discontinued due to this event. Bilirubin was increased to Grade 2 on Day 64. Patient decided to withdraw from the study and did not return for post treatment safety follow-up; consequently, outcome of the liver event remains unknown. She died 3 months after the end of treatment due to disease progression.
CBKM120F2302 – patient 3080012 (fulvestrant + 100 mg/d buparlisib)	53 year-old female patient with metastatic breast (liver, lung, bone and lymph-node metastasis), history of hypothyroidism, migraine, nausea, mood alteration, hot flashes, weakness, constipation and fibromyalgia; normal baseline liver chemistries. On Day 15, she developed Grade 1 ALT increase that worsened to Grade 2 on Day 39 (buparlisib/placebo dose reduced to 80 mg/d), and to Grade 4 on Day 46 upon which study treatment was permanently discontinued. Bilirubin was increased to Grade 2 on Days 53 and 55. The patient was taking levothyroxine for hypothyroidism, metamizole and ibuprofen for pain and clodronate for bone metastasis (before and during the study). The patient further had concurrent disease progression by RECIST on Day 50 (new liver lesions). The patient recovered from the event.
CBKM120F2302 – patient 5037006 (fulvestrant + 100 mg/d buparlisib)	54 year-old female patient with metastatic breast cancer (bone metastasis), history of vomiting/nausea, anemia, GERD, and elevated GGT (Grade 1) at baseline. On Day 43 she developed Grade 2 AST and Grade 1 ALT increase (treatment with buparlisib/placebo interrupted). Transaminitis worsened to Grade 4 on Day 50 upon which study treatment was permanently discontinued. Bilirubin was increased to Grade 2 from Day 50 to 56. The patient received ibuprofen for headache and fever (from Day 49), prophylactic piperacillin/tacobactam/vancomycin (from Day 50 to 53) and zoledronic acid for bone metastasis. The patient recovered from the event.
CLDE225X2114 – patient 1514005 (80 mg/d buparlisib + 400 mg/d LDE225)	71 year-old male patient with stage IV glioblastoma multiforme and no relevant medical history; normal baseline liver chemistries. On Day 44, he developed Grade 4 transaminitis and Grade 1 bilirubin increase upon which study treatment was permanently discontinued. Bilirubin briefly increased to Grade 2 on Day 57 based on local labs. Patient received paracetamol for pain, metoclopramide and ondansetron for nausea from Day 58 to 60; he was further on dexamethasone for seizure prophylaxis during the study. The patient recovered from the event.

In the randomized Phase 3 study [CBKM120F2302] in combination with fulvestrant, 13 vs 4 patients in the buparlisib vs placebo arm reported AST/ALT >3x ULN and total bilirubin >2x ULN regardless of causality and temporal relationship. Based on medical review, 5 out of these cases were consistent with Hy's law criteria, all of which were in the buparlisib arm. These 5 cases are part of the 8 total cases described above.

Table 6-X Criteria for interruption and re-initiation of BKM120/placebo treatment

These changes must be recorded on the Dosage Administration Record eCRF

Worst toxicity (CTCAE 4.03 Grade)**	**Dose Modifications for BKM120/placebo**
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 BKM120/placebo
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from BKM120/placebo
AST or ALT	
AST or ALT without bilirubin elevation > 2ULN Note: confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
Same grade as baseline (i.e. Grade 0 or Grade 1 (> ULN – 3.0 x ULN) if presence of liver metastasis)	Maintain dose level with LFTs* monitored per protocol
Increase from baseline Grade 0 to > 1.5 ULN or from baseline Grade 1 to Grade 2	Can continue treatment at ↓ 1 dose level
Increase of two grades from baseline (from baseline Grade 0 to Grade 2 or from baseline Grade 1 to Grade 3)	Omit dose until resolved to Grade 1 or less, then ↓ 1 dose level** If no recovery in ≤ 28 days, discontinue permanently BKM120/placebo
Grade 4 (> 20.0 x ULN)	Discontinue BKM120/placebo permanently
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue BKM120/placebo***
*(LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT) ** In case of recurring Grade 3 or higher toxicity after re-challenge, patients should be permanently discontinued	

Worst toxicity (CTCAE 4.03 Grade)**	**Dose Modifications for BKM120/placebo**
*** All patients with ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN in the absence of cholestasis ~~ULN~~ must immediately be withdrawn from BKM120/placebo and every attempt should be made to carry out the **liver event follow-up assessments** as described below in Section 6.2 Management f hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo and Section 7.2.X.X.X Viral hepatitis serology and other tests for hepatotoxicity follow-up). **Hepatic toxicity monitoring** (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT): **Cycle 1 and 2: every other week** (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT, or bilirubin* values **Cycle 3 and onward: monthly** or more frequently if clinically indicated In case of any occurrence of ALT/AST, or bilirubin* increase ≥ **grade 2** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ grade 1** In case of any occurrence of ALT/ AST, or bilirubin* increase ≥ **grade 3** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ grade 1**; hereafter the monitoring should be continued **every other week** or more frequently if clinically indicated **until the end of treatment with study medication** Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated **until resolved to ≤ grade 1 or stabilization** (no CTCAE grade change over 4 weeks).	

Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo

Criteria for interruption and re-initiation of BKM120/placebo treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in Section 6.2, Dose Modification (Table 6-X).

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 BKM120/placebo, 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
- Obtain PK sample, as close as possible to last dose of study drug if PK analysis is performed in the study. Record the date/time of the PK blood sample draw and the date/time of the last dose of BKM120/placebo prior to blood sample draw on the eCRF
- 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.

Patient demographics and other baseline characteristics
Furthermore the following assessments will be performed to assess the eligibility of the patient:

- Viral hepatitis serology [e.g. HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb] and other tests (see Section 6.2.4.X Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo and Section 7.2.X.X.X Viral hepatitis serology and other tests for hepatotoxicity follow-up)

Assessment types
Laboratory evaluations
Hepatotoxicity follow-up testing will be performed when needed (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 BKM120/placebo).

Table 1-7 Clinical laboratory parameters collection plan Test Category

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 6.2.4.X Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120/placebo and Section 7.2.X.X.X 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 BKM120/placebo, 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 BKM120/placebo for details.

Viral hepatitis serology includes the following:
- Hepatitis A IgM antibody and hepatitis A serology total
- Hepatitis B surface antigen, Hepatitis B Core Antibody (IgM) and viral RNA
- 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

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

Table 1-8 Number (%) of patients with Liver toxicity, regardless of study drug relationship, by preferred term and treatment – occurred at 100 mg/day in ongoing buparlisib studies

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

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

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

Please refer to the respective inclusion/exclusion criteria.

Mood disorders

Recently, a number of publications demonstrated that the modulation of AKT/GSK3 signaling pathway by neurotransmitters is important for the regulation of behavior (Beaulieu 2009). Preclinical studies conducted in rats to investigate the effect of buparlisib on different neurotransmitters have shown that repeated administration of buparlisib resulted in an enhanced

decrease in glutamate, dopamine, serotonin and epinephrine as well as in an enhanced increase in GABA and HIAA.

Psychiatric side effects events have been reported in patients treated with buparlisib and are currently under investigation. The current data does not allow the identification of any sign or symptom which could predict patient susceptibility to buparlisib induced psychiatric disorders. A broad range of AEs including (but not limited to) depression, anxiety, mood alteration, confusion, affective disorders, insomnia, hallucination, panic disorders, irritability or difficulties to concentrate have been reported.

Considering the initial symptoms reported during the first-in-man [CBKM120X2101] study, mood disorders have been analyzed based on HLGT 'Mood disorders and disturbances NEC' or HLGT 'Personality disorders disturbances in behavior' or HLGT "Psychiatric and behavioral symptoms NEC" or HLGT "suicidal and behaviors NEC". The frequency of mood disorders thus defined, regardless of study drug relationship, ranged from 6.3% in [CBKM120B2101] study to 50.0% in dose escalation part of [CBKM120X2107] study, however, the majority of events were of grade 1 or 2 severity (Table 1-7).

Table 1-7 Number (%) of patients with Mood disorders, regardless of study drug relationship, by preferred term and treatment occurred at 100 mg/day in ongoing buparlisib studies

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

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

Therefore, patients must be regularly and closely monitored for signs and symptoms of neuropsychiatric disorders with particular attention to changes in mood and personality. To support the identification and the assessment of psychiatric disorders, two self-assessment questionnaires, the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), are part of the protocol. Any AEs (symptom/diagnosis) should be accurately reported using CTCAE toxicity/grading. A consultation with a psychiatrist is strongly recommended for any psychiatric adverse event grade ≥ 1. Protocol guidelines further disqualify patients with an

active and/or history of major psychiatric disorder. Please refer to the respective inclusion/exclusion criteria.

Lung Toxicity/ Pneumonitis

Lung changes compatible with pneumonitis have not been observed in the preclinical setting. Among the current studies, pneumonitis was reported in five cases and interstitial lung disease in one further case. One case of pneumonitis had a fatal outcome in a complex clinical context, combining progression of lung metastases and possible infection with pneumocystis carinii or cytomegalovirus. Apart from this fatal case, the conditions were resolved or improving at the latest report (except one non-suspected SAE which was unchanged).

The currently available data still do not enable a clear assessment about the causal relationship of pneumonitis with buparlisib treatment. Newly appearing or significant changes in pulmonary symptoms (which cannot be explained by the underlying disease), should be carefully followed with appropriate management as per institutional guidelines and the guidelines provided in the protocol.

Please refer to Table 4-5 for a more detailed guideline on the diagnosis and management of Pneumonitis.

Hyperglycemia events

The PI3K/AKT pathway plays a significant role in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycemia is considered as an “on target” effect of buparlisib. Regular monitoring of FPG, HbA1c, and insulin C-peptide is implemented in buparlisib protocols to evaluate this pharmacodynamics effect. Transient increases of plasma glucose levels have been reported commonly in patients treated with buparlisib. Hyperglycemia observed at 100 mg/day, regardless of study drug relationship, in ongoing buparlisib studies are summarized in Table 1-8.

Table 1-8 Number (%) of patients with Hyperglycemia (narrow search), regardless of study drug relationship, by preferred term and treatment occurred at 100 mg/day in ongoing buparlisib studies

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

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

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

Detailed guidelines to monitor and manage patients who develop hyperglycemia are provided in Table 4-1.

Skin rash and hypersensitivity

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

representative number of patients treated with 100mg of buparlisib. In one study with nine evaluable patients, seven patients (77.8%) reported such events (Table 1-9).

Studies of buparlisib in combination with other agents tended to report slightly higher frequencies (e.g. combination with MEK inhibitor). The skin rashes seen have no typical location or distribution pattern, are mainly papulo-macular (only a minority are acneiform) and are frequently associated with pruritus. Events have been reversible after treatment interruption and/ or dose reduction. Effective medications have included antihistamines, topical corticosteroids and/or low-dose systemic corticosteroids (the latter should be used with caution due to the increased risk of hyperglycemia). There have been few cases reported of allergic reactions and DRESS (drug rash with eosinophilia and system symptoms), but these have not been of acute onset or of a severe nature.

Complementary information collected suggests that sun exposure may exacerbate the condition and should be avoided; however, genuine photosensitivity reaction has not been confirmed and no phototoxic potential has been seen pre-clinically. Patients are advised (e.g., in the written patient information) to avoid sun exposure, or take measures to protect themselves from intense sunlight, during study treatment.

Table 1-9 Number (%) of patients with Hypersensitivity, rash, regardless of study drug relationship, by preferred term and treatment occurred at 100 mg/day in ongoing buparlisib studies

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

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

Guidelines for the treatment of buparlisib induced hyperglycemia

Hyperglycemia is a common site effect of PI3K and also mTOR inhibitors. Hyperglycemia often occurs during the first weeks after treatment start and is dose-dependent. Transient increase of glucose levels have been observed in some patients. Regular monitoring of FPG to early identify hyperglycemia and prevent acute/sub-acute complications is important. Caution is warranted for

patients with history of DM, or taking corticosteroids, or with other severe medical conditions (e.g. infections), or patients who show potential acute signs such as poly-noctiuria, polidypsia, confusion, etc. Hyperglycemia management guidance includes patient education and dietetic measures/life-style changes as well as appropriate anti-diabetic medications as per investigator's decision and/or local guidelines.

Oral anti-diabetics such as metformin should be considered as first-line treatment for sustained and more severe hyperglycemia (other drugs as appropriate). Provided hyperglycemia is asymptomatic and there are no acute complications, sufficient time should be given to install optimal management (e.g. uptitrate metformin, addition of a second oral anti-diabetic agent to be considered as needed, etc.). Patients initiated on sulfonylurea or insulin should be instructed on how to recognize (and treat) hypoglycemia. Patients with history of DM, management should take prior anti-DM treatments into account. Note that some oral anti-diabetic drugs are CYP2C9 substrates and should be used with caution; others are CYP3A inducers or inhibitors and may be prohibited (see Appendix 1 and Appendix 2 for more details). Patients who develop Grade 3 or 4 or symptomatic hyperglycemia should be managed urgently as per standard clinical practice, with the goal of stabilizing glycemic control within 24 hours. More guidance on dose reductions and interruptions is provided in Table 3 above.

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.

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.

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 3.

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 Cycles 2, Day 1 of each subsequent cycle, and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self-reported questionnaires. Additional assessments may be done according to the clinical judgment of the investigator if desired.

Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is a class-effect observed with PI3Ki/mTORi agents. Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash) (refer to Table 3 for clinical management); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate comedication and treatment interruption if needed. Photographs of a skin rash event as well as skin biopsy are recommended, if possible. 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) to further assess rash if clinical appropriate.

Recommended therapies for skin toxicity events (refer to Table 3 for specific guidance according to the type of skin toxicity):

- Topical steroids of moderate potency (face and folds): triamcinolone 0.025%; aclometasone 0.05% (< 8 weeks continuously), for mild and moderate rashes.
- Topical steroids of high potency (trunk/extremities): fluocinonide 0.05%; clobetasol 0.05% cream or spray (< 8 weeks continuously), for mild and moderate rashes.
- Oral antihistamines (sedating, evening): diphenhydramine 25 to 50mg t.i.d; hydroxizine 25mg tid or q.i.d;
- Oral antihistamines (non-sedating, day time): fexofenadine 180mg q.d. or 60mg tid (monitor the use of this class of drugs since skin toxicity has also been reported)
- Oral corticosteroids: prednisone 0.5mg/kg or equivalent up to 5 days of treatment
- In case of mild acneiform rashes topical antibiotics: clindamycin 1% to 2%; erythromycin 1% to 2% (gel or solution formulation can be used, ointments cannot be used); metronidazole 1%; silver sulphadiazine.
- For more severe acneiform rashes oral antibiotics: doxycycline 100mg b.i.d.; minocycline 100mg b.i.d.; oxytetracycline 500mg b.i.d. for 6 weeks can be considered. If infection suspected (yellow crusts, purulent discharge, painful skin/nares), then switch to broad spectrum/gram negative antibiotics; consider skin swab for bacterial culture.
- Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
- For severe pruritus GABA Agonists: Gabapentin 300mg every 8 hours, or pregabalin 50 to 75 mg every 8 hours (to adjust of renal impairment) can be considered. Dose should be adjusted depending on patient's clinical condition be of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others AEs.

Dry skin has been reported, it is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, ammonium lactate cream 12% or salicylic acid cream 6% b.i.d.

Photosensitivity has been described in patients although preclinical experiments demonstrated that buparlisib has no potential phototoxic effect. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including regular use of sunscreen (factor 20 at least), wearing of sunglasses, using of hats, and protective clothes when outdoors.

Guidelines for the management of Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of PRES occurring under treatment with buparlisib. Signs and symptoms may include severe headache, confusion or seizures, altered consciousness, visual disturbances, with or without associated high blood pressure. Patients are instructed in the written patient information to inform their treating physician if they suspect such an event. Take appropriate measures in such cases to assess the signs and symptoms. If PRES is suspected based on the signs and symptoms, buparlisib should be interrupted and a brain MRI should be performed to confirm the diagnosis.

1.3.1.3.1.2 Human pharmacokinetic and metabolism data

Preliminary clinical pharmacokinetic data of buparlisib after single and multiple daily dosing are available from the first-in-human trial [CBKM120X2101]. Buparlisib was administered as a

capsule (doses ranging between 12.5 and 150 mg) and full pharmacokinetic profiles were collected on Day 1, Day 8 and Day 28 of Cycle 1.

Buparlisib was rapidly absorbed, with the median time to reach the peak plasma concentration (Tmax) ranging from 1.0 to 1.75 hours after administration. Tmax was independent of dose and was not altered after multiple oral doses. Variability in systemic drug exposure was moderate at all dose levels. At 100 mg the variability in systemic drug exposure and Cmax (CV %) at steady-state was moderate, about 36% and 25%, respectively.

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

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

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

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

In the current study, corticosteroids and other CYP3A4 inducers will be prohibited in order to maintain buparlisib exposure in the expected range. In addition, anti-acids will be dosed at least one hour after buparlisib administration to avoid a decrease of pH during the absorption phase of buparlisib and thus avoid any possible solubility limitations.

1.3.1.3.1.3 Clinical efficacy data

Sixty six patients were evaluable for response in study [CBKM120X2101] where all patients in the expansion cohort were required to have mutated and/or amplified PIK3CA and/or mutated PTEN or null/low PTEN protein expression: partial tumor responses (PR) were observed in 3 patients, one of which was a RECIST v1.0 confirmed PR in a patient with triple negative breast cancer and the other 2 patients' responses were not confirmed (1 patient with metastatic breast cancer and 1 patient with parotid carcinoma) (Graña 2011).

The first patient was a 61 year-old female with poorly differentiated ductal metastatic breast cancer assessed as triple negative (ER-, PgR-, HER2-), PI3KCA wild type, PTEN IHC positive. Since 2006 she received many previous anticancer agents (cyclophosphamide, doxorubicin,

gemcitabine, docetaxel, paclitaxel, vinorelbine, capecitabine, etoposide, anastrozole). As progressive disease developed (bulky lymph node involvement and local breast relapse), she was enrolled (April 2009) in the Phase I study of buparlisib in the 100 mg/day cohort. A metabolic response (61% decrease in SUV) was observed after 2 cycles, followed by a RECIST partial response (66% tumor shrinkage) after 4 cycles. This patient continues to receive treatment beyond 32 cycles.

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

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

As of the data cut-off 04July2011, preliminary analysis shows forty-five percent of patients (30 of 66 evaluable) had stable disease as their best response, with 20 patients (30%) having a disease stabilization of 3 months or longer. A trend towards better activity (long-term stabilizations) has been observed at the higher dose cohorts, also expressed in metabolic FDG-PET response. However, considering the impact of a PI3K inhibitor on glucose metabolism, further data are needed to understand whether the current FDG-PET assessment data can be used as a predictive factor for efficacy.

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

With regards to the PI3K pathway activation, two of the three responders described above had a cancer with a PIK3CA mutation. Moreover, 18 patients had a stable disease lasting for 16 weeks or longer, including 8 patients who had tumors with an activated PI3K pathway. These data are promising and continued exploration of the activity of buparlisib in patients with activated PI3K pathway is warranted.

More specifically, in [CBKM120X2101], 25.3% (21/83) of patients had metastatic breast cancer. At the cut-off date of July 4th, 2011, twenty breast cancer patients were evaluable for objective tumor response by RECIST 1.0. Two breast cancer patients (11%), described above exhibited partial responses. For these 2 patients, the treatment duration was 27+ (ongoing) and 5 months, respectively. An additional 8 breast cancer patients (40%) had stable disease. Median progression-free survival was 60 days and the 6-month PFS rate was 33% (Rodon 2011).

Other than [CBKM120X2101], two trials are ongoing in breast cancer patients with preliminary data available:

- In [CBKM120X2107], buparlisib is combined with trastuzumab in metastatic breast cancer patients with trastuzumab resistance. As of September 30, 2011, out of 17 patients enrolled, 2 PR and 8 SD were observed in the dose escalation portion of this study, with a disease control rate (CR+PR+SD) of 59%. (Saura 2011).
- Buparlisib has been combined with letrozole in ER+ post-menopausal breast cancer patients (Mayer 2011). Out of the 20 patients enrolled, 12 were evaluable for efficacy; 1 PR, and 7 SD were observed. Over 50% of patients had >25% reduction in their peak SUV at the 2-week FDG-PET scan.

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

1.3.2 Capecitabine

Capecitabine is a prodrug that is enzymatically converted to 5-fluorouracil in the tumor where it inhibits DNA synthesis and slows growth of tumor tissue (Xeloda package insert). Capecitabine is approved in both colorectal and breast cancer. Capecitabine demonstrated single-agent activity in subjects with MBC with an ORR of about 20% in subjects whose disease had progressed during or following anthracycline and taxane-based therapy (Xeloda package insert). Capecitabine is also indicated as a combination treatment with docetaxel in early-line treatment for MBC and in combination with ixabepilone or lapatinib as second-line treatment after failure of prior anthracycline and taxane-containing chemotherapy (Xeloda package insert).

The recommended, approved dose of capecitabine is 1250 mg/m^2 daily BID for 14 days, followed by 7 days without treatment (Xeloda package insert). This dose/schedule necessitates dose interruptions or reductions in approximately 30% of patients, and in clinical trials, approximately 17% of patients discontinued the drug due to toxicities (primarily hand-foot syndrome, diarrhea and stomatitis) (Mackean 1998; O'Shaughnessy 2001).

There have been isolated case reports of responses to single agent capecitabine in patients with breast cancer-related CNS metastases (Ekenel 2007; Hikino 2006; Rogers 2004; Wang 2001; Fabi 2006; Tham 2006). In addition, in a phase II trial of patients with HER2+ MBC with CNS metastases, the combination of capecitabine plus lapatinib was associated with a higher objective response rate (20%) compared with 6% observed with lapatinib alone (Lin 2009). Further, this combination produced a 66% partial CNS response rate in patients with previously untreated HER2+ CNS metastases in the phase II LANDSCAPE trial (Bachelot 2013).

1.3.3 Buparlisib in combination with capecitabine

Investigators at the University of North Carolina and Duke are conducting a phase I study of capecitabine plus buparlisibin patients with MBC. Although the study is not yet completed, 16 patients have been enrolled as of January 3, 2013. Based on assessment of toxicities in cycle 1, the investigators believe that the recommended phase II dose from this study will likely be capecitabine 1000 mg/m^2 PO BID 14 days on and 7 days off plus buparlisib 100 mg PO QD. Additional patients are being enrolled to this dose level presently. Dose limiting toxicities (DLT) to date have included one patient each with psychosis, photosensitivity "sunburned" rash, fatigue, and mucositis. Several patients who did not have a cycle 1 DLT, and whose disease had not progressed, withdrew from study therapy due to capecitabine-related toxicities including

diarrhea and hand foot syndrome, which occurred after cycle 1. Several patients needed a dose reduction of capecitabine in cycles 2-5, and dose reductions of buparlisib to 80 mg PO QD were required in some patients due to grade 2 psychiatric or cognitive side effects. Evidence of antitumor activity has been observed in triple negative and ER+ MBC patients. Overall, administration of the combination of capecitabine and buparlisib is feasible with doses of the two agents that are their single agent MTDs. Toxicities observed to date have been generally manageable with dose reduction although some patients have withdrawn from study therapy due to cumulative toxicity (Claire Dees, MD. personal communication).

1.3.4 Buparlisib in combination with trastuzumab

A phase Ib/II trial by Pistilli et al ESMO 2012 combining trastuzumab plus buparlisib (100mg QD) showed acceptable safety in 52+ pts with basically no overlapping toxicities (Pistilli 2012). Of note, 5 patients had brain metastasis at study entry and 2 had SD still ongoing at the time of the abstract; 2 others had SD for 90 and 106 days and the fifth was not evaluable.

1.4 Study Rationale

CNS metastases occur with high frequency in patients with metastatic MBC, developing in approximately one-fourth to one-half of patients. Currently there are no effective systemic therapies that have been shown to improve OS for patients with MBC with brain metastases. (see Section 1.1.1) Thus, there is an urgent unmet need for more effective treatments for this patient population.

Dysregulation of the PI3K signaling pathway occurs in the majority of MBCs, through a variety of mechanisms including mutation of PIK3CA or PTEN, or loss of PTEN or INPP4B, as well as through activation by upstream receptor activation. PTEN loss and activation of PI3K signaling has also been documented specifically in MBC brain metastases, making inhibition of this pathway an attractive therapeutic strategy for investigation. (see section 1.2.1)

Capecitabine and buparlisib have both individually demonstrated the ability to penetrate the blood-brain barrier, and have shown activity in MBC, making this a rational combination to evaluate for the treatment of MBC brain metastases. In addition, this combination is currently being evaluated in a phase I study in MBC, including patients with MBC, with evidence of activity as well as tolerability. (see Section 1.3.3)

Given this background, we have decided to proceed with a phase II study to test the combination of capecitabine plus buparlisib in metastatic breast cancer with HER2+ or ER+/HER2- or triple negative brain metastases. The purpose of this study is to evaluate the effect of buparlisib plus capecitabine on clinical benefit rate in this patient population.

1.4.1 Rationale for dose selection

Buparlisib will be administered at a dose of 100 mg orally (PO) daily, the MTD/RP2D determined in single agent ([CBKM120X2101] and [CBMK120X1101]) and combination ([CBKM120X2107], [CBEZ235A2118] and [CBKM120XUS13T]) studies (Buparlisib Investigator Brochure). This dose has also shown preliminary tolerability in combination with capecitabine in the ongoing phase I study in MBC. Capecitabine will be administered at a dose

of 1000 mg/m^2 PO BID (rounded down to the nearest 500 mg pill) 14 days on and 7 days off, based on the recommended phase II dose determined in the phase I study of capecitabine plus buparlisib in MBC (Claire Dees, MD. personal communication).

2 Study objectives

Primary Objectives

- To determine the clinical benefit rate (CBR) based on local investigator assessment associated with buparlisib once daily plus capecitabine (1000 mg/m^2 PO BID 14 days on/7 days off) in patients with metastatic breast cancer with a brain metastasis at least 5mm in size following whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) or both. The target lesion that is at least 5mm in size must not have undergone treatment with SRS and may represent residual disease following SRS or WBRT, or may represent progression of disease following SRS or WBRT. Clinical benefit rate is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) or stable disease (SD) in the CNS lasting at least 24 weeks based on local investigator assessment.

Secondary Objectives

- To assess ORR in the CNS based on local investigator assessment associated with buparlisib plus capecitabine.
- To assess median time to progression (TTP) associated with buparlisib plus capecitabine.
- To determine median overall survival (OS) associated with buparlisib plus capecitabine.
- To determine if buparlisib plus capecitabine prolongs OS compared with expected survival of patients with brain metastases, estimated using the breast-GPA (See Appendix 1).
- To characterize the safety and tolerability of buparlisib plus capecitabine, with or without trastuzumab.
- To assess median time to deterioration of neurologic function.
- To monitor changes in symptom occurrence using the M.D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT), and to provide results of PHQ-9 Depression Scale.
- To investigate whether there is a correlation between PI3K pathway-related biomarkers and clinical response.

3 Exploratory Investigational Plan

3.1 Overall Study Design

This is a Phase 2, multicenter, single-arm study to determine the efficacy and safety of buparlisib plus capecitabine in approximately 42 patients with metastatic breast cancer with measurable brain metastases at least 5mm in size following WBRT or SRS or both. The target lesion that is at least 5mm in size must not have undergone treatment with SRS and may represent residual

disease following SRS or WBRT, or may represent progression of disease following SRS or WBRT.

This study will consist of 2 phases: a Screening Phase where the informed consent will be collected and eligibility criteria will be assessed followed by a Treatment Phase that includes end-of-treatment follow-up assessments. The Screening Phase will include assessments before the first dose of study drugs (Cycle 1/Day 1) to establish eligibility and baseline values. The Treatment Phase will commence for each subject with the first dose of buparlisib plus capecitabine, with or without trastuzumab, and continue through the end of treatment. After discontinuing all study treatment, the patient will be followed for a mandatory 30-day safety follow-up, efficacy (tumor assessments, if applicable) follow-up and survival follow-up.

During the treatment phase:

- Patients with HER2- MBC will receive buparlisib orally (PO) at a dose of 100 mg daily continuously in combination with capecitabine 1000 mg/m^2 PO BID 14 days on/7 days off.
- For patients with HER2+ MBC, standard every 3-weekly trastuzumab (6 mg/kg IV) will be added to the capecitabine/buparlisib.

Patients will receive treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients will be followed for survival regardless of treatment discontinuation for any reason for up 2 years from date of registration (except if consent is withdrawn or patient is lost to follow-up).

Note: Information from procedures that may have been previously performed as part of the patient's routine disease care (prior to enrolling in the trial) is allowed to be used to satisfy inclusion criteria as long as the procedures were performed within 28 days of registration.

Screening phase

All patients will undergo screening assessments to determine study eligibility. Within 28 days before initiation of treatment, the patient will provide a signed informed consent form prior to any study related activities. All screening evaluations must be performed during the screening period (day −28 to day −1). Receptor status may be obtained anytime before enrollment on study. Collection and shipment of tumor sample (new biopsy or archived tissue) to designated lab (check the CTI) should occur as soon as possible and no later than Day −1. Check Table 4-12 for details of tests to be done at screening.

Screening procedures are to be performed within 28 days of the start of study treatment. Receptor status may be obtained any time before enrollment on study. Baseline values for those assessments (e.g., physical examination, ECOG performance status, weight, vital signs, hematology, biochemistry and fasting plasma glucose) may be used for Cycle 1 assessments as long as they are performed within 2 weeks prior to the patient receiving their first dose of the of study drug.

Treatment phase

Once inclusion and exclusion eligibility criteria have been confirmed, study treatment will be initiated. Patients will receive buparlisib orally (PO) at a dose of 100 mg daily continuously in combination with capecitabine 1000 mg/m^2 PO BID 14 days on/7 days off, then repeat the cycle. Patients with HER2+ MBC will also receive trastuzumab by IV administration every 3 weeks.

Capecitabine needs to be rounded down to the nearest 500 mg pill. Buparlisib and capecitabine dose modifications will be allowed (see Section 4-1). Safety will be monitored as outlined in Section 4-3.

Cycle treatment and evaluations will be performed during therapy at the start of each cycle, unless otherwise specified. Cycle 2 and subsequent cycles, has a window of +/-3 business days (after the scheduled time) for treatment administration and cycle assessments (e.g., the physical examination, performance status (ECOG), weight, vital signs, and labs) during the study treatment. Any delay within this window is NOT a deviation.

Patients will receive treatment until disease progression (assessed by RECIST 1.1), unacceptable toxicity, death or discontinuation from treatment for any other reasons. Efficacy and safety monitoring will continue as per the visit schedule (Table 4-12). Tumor assessments will be performed every 8 weeks after treatment initiation date until clinical or radiological progression. Disease progression in the brain and other sites should always be documented radiologically, adding an earlier than planned imaging time point for tumor assessments as clinically indicated.

Note: Cycle 1 only, the baseline values for those assessments (e.g., the physical examination, performance status (ECOG), weight, vital signs hematology, biochemistry, and fasting plasma glucose,) that are to be done for screening may be used for Cycle 1 assessments as long as they are completed within 2 weeks prior to the patient receiving their first dose of study drug. If more than 2 weeks have elapsed since the baseline assessment, the assessment must be repeated. Assessments need to be put in the order in which they appear in eCRF. Treatment must begin within 5 working days after patient registration to the study, not including weekends or holidays.

End of Treatment Phase

After the end of the treatment visits, all patients will be followed up for safety up to 30 days after the last dose of study treatment (buparlisib plus capecitabine). There is window of +/- 7 business days for end of treatment assessments. Any delay within this window is NOT a deviation. End of treatment will continue as per the visit schedule (Table 4-12).

Follow up phase

After the end of the treatment visits, all patients will be followed up for safety up to 30 days after the last dose of study treatment (buparlisib plus capecitabine).

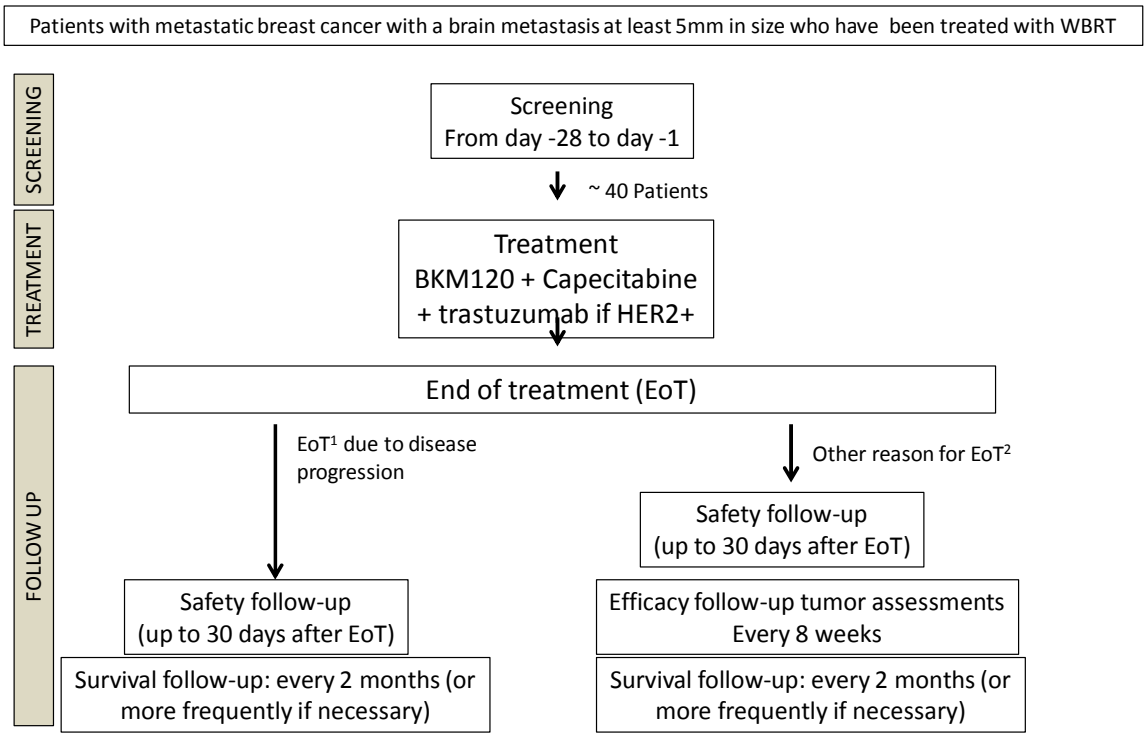
All patients who discontinue from study treatment due to disease progression must have their progression clearly documented according to the criteria specified in RECIST 1.1.

If a patient did not discontinue study treatment due to disease progression, death, adverse event, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent for efficacy follow-up then tumor assessments should continue to be performed every 8 weeks until the start of new anti-cancer therapy, disease progression, death, lost to follow-up or withdrawal of consent for efficacy follow-up.

All patients will be followed for survival every 2 months from last date of treatment regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up) until death or for up to 2 years from date of registration. Survival information can be obtained via phone and information will be documented in source document.

There is window of +/- 7 business days for end of treatment assessments. Any delay within this window is NOT a deviation. For details on required assessments, please refer to Table 4-12.

Figure 3-1 Study design



[1] End of treatment (EoT) is due to disease progression, start of new cancer therapy, lost to follow-up or withdrawal of consent for efficacy follow-up
[2] EoT is for reasons other than disease progression, lost to follow-up or withdrawal of consent for efficacy follow-up or started new anti-cancer treatment

Definition of end of the study

The end of study is defined as the time point when data collection will stop and the final analysis of the study will occur. The end of study will be declared depending on the results of the primary analysis.

3.2 Study Population

3.2.1 Patient population

The primary analysis patient population consists of patients with MBC with a non-progressing brain metastasis that is at least 5mm in size and who have undergone treatment with WBRT or SRS or both at any time for their brain metastases and who do not have evidence of impending visceral crisis outside of brain. The target lesion that is at least 5mm in size must not have undergone treatment with SRS and may represent residual disease following SRS or WBRT, or may represent progression of disease following SRS or WBRT. Evidence of progression of disease following WBRT or SRS is allowed but is not required. Patients may be symptomatic as long as ECOG performance status is ≤2. There is no limit on the number of chemotherapy regimens previously received and prior treatment with capecitabine is allowed. The patients

must not have active cardiac disease, or clinically significant GI disease that impairs GI function. The patients must provide tumor tissue (archival or new biopsy) for the analysis of PI3K pathway-related biomarkers unless previously discussed with the study principal investigator.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study. Eligible patients must have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria.

The patients are not permitted to participate in additional parallel investigational drug or device studies.

3.2.2 Registration procedures

Written documentation of full IRB and FDA approval must be on file before a patient can be registered. The registration process begins when the coordinator has obtained a signed informed consent. Please enter patient demographics into the Clinical Trial Management System (CTMS); this is the Web-based intranet system for the delivery of trial information between Delta and used across all sites. A UPN will be assigned to the patient at that time. Entering a patient into CTMS does not signify that you have registered the patient in the study. If you have any difficulty with CTMS please contact the Clinical Trial Manager.

Once the patient has an UPN number, the coordinator can go to their Patient Report and select the patient that they want to register. Located to the left of the patient's UPN will be the letters "Reg" in blue. The coordinator will click on the blue "Reg" to open up that patient's information. Each page that needs to be completed will be in yellow. The site will answer the questions on the Inclusions and Exclusions. Once all questions on each page are answered, that page will turn green. Once all the pages turn green, click on the "verify data" tab, then click the "register" tab. The register page will open, "click to register". An ID number will be directly assigned. For any difficulties with entering the data, please contact the Project Manager of the study.

Treatment must begin within 5 working days after the patient's registration on the study, not including weekends or holidays.

3.2.3 Inclusion and exclusion criteria

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

Inclusion criteria

1. Age ≥ 18 years
2. Female
3. Histologically and/or cytologically confirmed diagnosis of inoperable breast cancer
4. ER+/HER2- OR HER2+ OR triple-negative breast cancer, assessed as ER-, PgR-, and HER2-negative by local laboratory testing; HER2 negative status (based on most recently analyzed biopsy) is defined as IHC status of 0, 1+ or 2+ (if IHC 2+, a negative FISH test is required, i.e., HER2 FISH ratio < 2.0 with an average HER2 copy number <4.0 signals/cell); ER-negative and PR-negative status is defined as ER and PgR <1% nuclei positive by IHC (per ASCO guidelines). HER2-positive status is defined as 3+ staining in ≥10% of cells by immunohistochemistry or a HER2/CEP17 ratio ≥2 or an average of ≥6 HER2 gene copies per cell by in situ hybridization (ISH) according to the 2013 ASCO/CAP guidelines
5. At least one CNS lesion that is at least 5mm in size in at least one dimension in the setting of prior WBRT or SRS or both:
   - Prior WBRT or SRS or both is required and may have been administered at any time in patient's treatment history. Patients must have completed WBRT at least 3 weeks prior to study entry and a minimum of a 5 days window is required following SRS before beginning study therapy.
   - The target lesion that is at least 5mm in size must not have undergone treatment with SRS and may represent residual disease following SRS or WBRT, or may represent progression of disease following SRS or WBRT or both.
6. ECOG performance status ≤ 2
7. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb >9 g/dL
8. Total calcium (corrected for serum albumin) within normal limits (biphosphonate use for malignant hypercalcemia control is not allowed)
9. Magnesium ≥ the lower limit of normal
10. Potassium within normal limits for the institution
11. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal range (or ≤ 3.0 x upper limit of normal (ULN) if liver metastases are present)
12. Serum bilirubin within normal range (or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with known Gilbert Syndrome)
13. Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
14. Serum amylase ≤ ULN
15. Serum lipase ≤ ULN
16. Fasting plasma glucose ≤ 120 mg/dL (6.7 mmol/L)
17. Negative serum pregnancy test within 72 hours before starting study treatment in women with childbearing potential
18. INR ≤ 2
19. Life expectancy > 12 weeks
20. Available tissue (blocks and/or slides) samples unless discussed in advance with study principal investigator

21. Patient is able to swallow and retain oral medication
22. Signed most recent patient informed consent form
23. Signed Patient HIPAA Authorization Form

Exclusion criteria

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

1. Patient received prior treatment with a PI3K inhibitor.
2. Patient with known hypersensitivity to buparlisib, capecitabine, or their excipients.
3. Patient has evidence of impending herniation on baseline brain imaging.
4. Patient has evidence of diffuse leptomeningeal disease on brain MRI or by previously documented CSF.
5. Patients has acute or chronic liver, renal disease or pancreatitis (liver metastases are allowed)
6. Patients has a mood disorder as judged by the Investigator or a psychiatrist, or as a result of patient's mood assessment questionnaire (PHQ-9 and/or GAD-7):
    - Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others) or patients with active severe personality disorders (defined according to DSM- IV) are not eligible**. Note: for patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.**
    - ≥ CTCAE grade 3 anxiety
    - Meets the cut-off score of ≥ 12 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or selects a positive response of "1, 2, or 3" to question number 9 regarding potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)
7. Patients has diarrhea ≥ CTCAE grade 2
8. Patients with uncontrolled hypertension defined as systolic blood pressure 170 or greater or diastolic blood pressure over 100.
9. Patient has active cardiac disease including any of the following:
    - Left ventricular ejection fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - QTc > 480 msec on screening ECG (using the QTcF formula)
    - Angina pectoris that requires the use of anti-anginal medication
    - Ventricular arrhythmias except for benign premature ventricular contractions
    - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
    - Conduction abnormality requiring a pacemaker
    - Valvular disease with document compromise in cardiac function
    - Symptomatic pericarditis

10. Patient has a history of cardiac dysfunction including any of the following:
    - Myocardial infarction within the last 6 months, documented by persistent elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LVEF function
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
11. Patient has poorly controlled diabetes mellitus or steroid-induced diabetes mellitus
12. Patient has other concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
    - Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude pneumonitis or pulmonary infiltrates.
13. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of buparlisib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with unresolved diarrhea will be excluded as previously indicated
14. Patient was treated with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GM-CSF) $\leq$ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued
15. Patient is currently receiving treatment with medication with a known risk to prolong the QT interval or inducing Torsades de Pointes and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug. Please refer to Table 3-2 or a list of prohibited QT prolonging drugs with risk of Torsades de Pointes.
16. Patients receiving chronic treatment with steroids or another immunosuppressive agent. Patients must have been off all corticosteroids (except for physiologic doses of hydrocortisone as replacement therapy) for at least 2 weeks prior to study entry.
    - **Note:** Single doses, or topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed.
17. Patient has taken herbal medications and certain fruits within 7 days prior to starting study drug. Herbal medications include, but are not limited to St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Fruits include the CYP3A inhibitors Seville oranges, grapefruit, pummelos, or exotic citrus fruits. Regular orange juice is permitted.
18. Patient is currently treated with drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Please refer to Table 4-8 for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).

19. Patient received chemotherapy or targeted anticancer therapy ≤ 3 weeks (6 weeks for nitrosourea, antibodies or mitomycin-C) prior to starting study drug, and have related side effects must recover to a grade 1 or less before starting the trial
20. Patient received any continuous or intermittent small molecule therapeutics (excluding monoclonal antibodies) with ≤ 5 effective half lives prior to starting study drug or who have not recovered from side effects of such therapy
21. Patient received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
22. Patient underwent major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
23. Patient is currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant.
24. Patient is pregnant or breast feeding or is of reproductive potential and not employing an effective method of birth control.
    - Note: Double barrier contraceptives must be used through the trial by both sexes. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment.
    - Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [***for US only***: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
    - Note: Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during treatment for 4 weeks (5 T1/2) after stopping treatment. The highly effective contraception is defined as either:
        1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
        2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that patient.
4. Use of a combination of any two of the following (a+b):
   a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
   b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
   - Note: Oral contraception, injected or implanted hormonal methods are not allowed as buparlisib potentially decreases the effectiveness of hormonal contraceptives.

25. Patient has known diagnosis of human immunodeficiency virus (HIV) infection
26. Patient has history of another malignancy within 5 years, except cured basal cell carcinoma of the skin or excised carcinoma in situ of the cervix
27. Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator
28. Patient is concurrently using other approved or investigational antineoplastic agent.
29. Patient taking or needing enzyme-inducing anti-epileptic medication.
30. Patients with an acute viral hepatitis or a history of chronic or active HBV or HCV infection

4 Treatments

4.1 Interruption or Discontinuation of Treatment

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Any changes in buparlisib or capecitabine administration must be recorded on the eCRF. If administration of buparlisib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 4-0 and Table 4-1. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0. (CTCAEv4.0), (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). The dose of buparlisib does not need to be reduced for toxicities that the physician believes are due to capecitabine.

Capecitabine dose modification guidelines are described in Section 4.1.3. Please refer to the local approved prescribing information. 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. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle. The dose of capecitabine does not need to be reduced for toxicities that the physician believes are due to buparlisib.

Trastuzumab dose modifications will be per physician's discretion and standard of care..

If the administration of buparlisib or capecitabine is interrupted for reasons other than toxicity, then treatment with the respective study drug may be resumed at the same dose. The same applies if the patient experiences an unacceptable toxicity not specifically described, provided this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

If one or both study drugs are being withheld due to toxicity, scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the held study drug), as described in Table 4-12. If administration of buparlisib or capecitabine dosing is held for more than 21 days, then this withheld study drug should be permanently discontinued. Patients who permanently discontinue one of the withheld study drugs for any reason other than disease progression may continue the other study drug as part of the trial therapy at the investigator's discretion.

Table 4-0 Buparlisib dose level modification guidelines

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

* Starting Dose

Table 4-1 Criteria for interruption and re-initiation of Buparlisib treatment

Recommended Dose Modifications for Buparlisib	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

Recommended Dose Modifications for Buparlisib	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
HEPATIC	
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	Will be fractionated if elevated
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level • If resolved in > 7 days discontinue patient from study treatment
Grade 4 (> 10.0 x ULN)	Omit dose and discontinue patient from study treatment
AST or ALT	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 3.0 - 5.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ grade 1, then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1 then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1 , then ↓ 1 dose level
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue study treatment permanently.
* LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. **Monitoring** (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT.	

Recommended Dose Modifications for Buparlisib	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
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 every at least 2 weeks

Grade 2 (>160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	• If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria) manage as for Grade 3 hyperglycemia (see below).
	• If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2:
	  • maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1
	  • initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if no improvement after several days
	  • instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study
	  • If FPG does not resolve to ≤ Grade 1 within 14 days after institution of appropriate anti-diabetic treatment reduce 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:

Recommended Dose Modifications for Buparlisib	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
	• 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 reduce 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

Recommended Dose Modifications for Buparlisib	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
	• 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).

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

Recommended Dose Modifications for Buparlisib	
Worst toxicity (CTCAE Grade)**	**Recommended Dose Modifications**
OTHER	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from buparlisib
Other non-hematological adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study Note: Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic
Pneumonitis	See Table 4.6
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.	

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 except in presence of suicidal ideation where dose must be interrupted and psychiatric consultation is required to provide 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 except in presence of suicidal ideation where dose must be interrupted and psychiatric consultation is required to provide 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)**

Skin toxicity	
Rash (maculo-papular)	
Grade 1 **(<10% body surface area BSA; no associated erythema or pruritus)**	**Maintain dose level. Consider to initiate appropriate skin toxicity therapy, e.g. with topical corticosteroids b.i.d. and oral antihistamines**
Grade 1	**Maintain dose level. Consider to initiate appropriate skin toxicity therapy with antihistamines and topical corticosteroids**

Grade 2
(10 to 30% BSA and associated with erythema or pruritus; limited instrumental activities of daily living (ADL))
	Tolerable Grade 2:
	• **Initiate/intensify appropriate skin toxicity therapy, e.g. with topical steroids b.i.d. and oral antihistamines.**
	• **Maintain dose level.**
	Intolerable Grade 2:
	• **Omit dose and initiate/intensify appropriate skin toxicity therapy, e.g. with topical steroids b.i.d., oral antihistamines and oral steroids.**
	• **First occurrence:**
	  • **If resolved to grade ≤ 1 in ≤ 2 weeks, maintain dose level.**
	  • **If resolved grade ≤ 1 in more than 2 weeks, ↓ 1 dose level.**
	• **Consider continuing skin toxicity therapy up to 2 weeks after re-introduction of BKM120/placebo. In case of flare after cessation of skin toxicity therapy, consider prompt re-implementation.**
	Second occurrence: omit dose and follow treatment guidance above,
	• **Once resolved to grade ≤ 1, ↓ 1 dose level**

Grade 3 **(Macules or papules covering >30%BSA with or without symptoms)**	• **Omit dose and initiate/intensify appropriate skin toxicity therapy, e.g. with topical steroids b.i.d., oral antihistamines and oral steroids.** • **Once resolved to grade ≤ 1, ↓ 1 dose level.** • **Consider continuing skin toxicity therapy up to 2 weeks after re-introduction of BKM120/placebo. In case of flare after cessation of skin toxicity therapy, consider prompt re-implementation**
Grade 4 **(including other skin toxicity than maculo-papular rash)**	**Permanently discontinue patient from BKM120/placebo**

Acneiform rash	
Grade 1 **(<10% body surface area BSA; no associated erythema or pruritus)**	**Maintain dose level. Consider to initiate appropriate treatment, e.g. with topical steroids (moderate potency) and topical antibiotics b.i.d.**

Grade 2
(10 to 30% BSA and associated with erythema or pruritus; limited instrumental activities of daily living (ADL))
	Tolerable Grade 2:
	• **Same management as Grade 1.**
	Intolerable Grade 2:
	• **Omit dose and initiate/intensify appropriate skin toxicity therapy, e.g. with oral antibiotics for 6 weeks; stop topical antibiotics if being used and start with topical steroids of moderate potency.**
	  • **If resolved to grade ≤ 1 in ≤ 2 weeks, maintain dose level.**
	  • **If resolved grade ≤ 1 in more than 2 weeks, ↓ 1 dose level.**
	Second occurrence: omit dose and follow treatment guidance above
	• **Once resolved to grade ≤ 1, ↓ 1 dose level**

Grade 3 **(>30% BSA And associated with pruritus; limiting self ADL)**	• **Omit dose and initiate/intensify appropriate skin toxicity therapy, e.g. with oral antibiotics for 6 weeks potency.** • **If infection suspected (yellow crusts, purulent discharge, painful skin / nares) then switch to broad spectrum/gram negative antibiotics; consider skin swab for bacterial culture; add topical steroid of moderate.** • **Once resolved to grade ≤ 1, ↓ 1 dose level.**
Grade 4 **(Papules and/or pustules covering any % BSA, associated with symptoms or not but associated with extensive superinfection)**	**Permanently discontinue patient from BKM120/placebo**
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.** **These changes must be recorded on the Dosage Administration section of the patient record.**	

4.1.1.3 Monitoring of buparlisib suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 3-1, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study. If the patient requires more than 2 dose reductions, the patient should be discontinued from the study (i.e., patients cannot be treated below dose level -2). All patients must be followed for adverse events and serious adverse events for 30 days following the last dose of buparlisib. All SAEs must be reported to Delta as detailed in Section 4.3.7.

4.1.2 Known Undesirable Side Effects of Buparlisib

4.1.2.3 Neuropsychiatric events

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

In order to lower the risk of experiencing significant mood alterations within the proposed study, cancer patients with an active or history of major depressive episode, bipolar disorder, obsessive-compulsive disorder, schizophrenia, a history of suicide attempt or ideation, or homicide/homicidal ideation as judged by the investigator and/or based on recent psychiatric assessment will not qualify for study participation. Patients with corresponding symptoms CTCAE Grade ≥ 2 should immediately be examined by a psychiatrist and closely followed medically. Medical treatment with mood stabilizers (2nd generation antipsychotics) such as olanzapine and quetiapine may be applied as per investigator's discretion and following consultation with a psychiatrist.

4.1.2.3.1 Management of mood alteration

Patient self-rating mood questionnaires PHQ-9 (depression) and GAD-7 (anxiety) will be administered by the study nurse or CRC and will be used:

- to support assessment of eligibility at Screening
- to monitor for newly occurring or worsening mood alterations during the study.

The following grading system will be used for this study (Table 4-2):

Table 4-2 Toxicity grading based on mood questionnaire scores

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

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

During the study, patients who meet the cut-off score of ≥ 10 (≥ CTCAE grade 2 mood alteration) in either questionnaire or who indicate a positive response by selecting '1, 2, or 3' to question number 9 on the PHQ-9 (Table 4-4) must see a psychiatrist for diagnosis and determination of most appropriate medical treatment. For anxiety, this applies only if status has worsened from baseline. Patients who experience ≥ grade 2 mood alteration will be followed twice weekly by the patient self-rating mood scale and will be seen weekly by the psychiatrist until resolved ≤ grade 1 or baseline (for anxiety). Questionnaire responses will be checked at weekly visits until resolution to Grade 1 or baseline (for anxiety).

Table 4-3 GAD-7 anxiety scale

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

Column totals: _____ + _____ + _____ + _____

= Total Score _____

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

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

Table 4-4 PHQ-9 depression scale

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

= Total Score _____

4.1.2.4 Hyperglycemia

In preclinical studies, insulin/glucose homeostasis was impacted in various species (mice, rats, dogs), as expected from the mode of action of buparlisib (Buparlisib Investigators Brochure). In both rats and dogs, at the doses used in the 4-week studies, these effects were minimal. However, in mice treated at high doses (30 or 60 mg/kg/day) a clear induction of insulin resistance/insensitivity was observed, without clear influence of the dose or the time point of testing. Histopathologic changes were seen in animal pancreas and liver samples which are in concordance with this activity.

Grade 4 Hyperglycemia was also observed in an ongoing Phase Ia study of buparlisib in patients with solid tumors (CBKM120X2101). Therefore, no patients with uncontrolled diabetes mellitus will be enrolled in this study. In all patients, fasting plasma glucose will obtained at screening and will be monitored throughout the trial. For the treatment of glucose disturbances occurring under buparlisib treatment investigators are advised to adhere to the protocol guidelines outlined in Table 4-1.

4.1.2.4.1 Management of Hyperglycemia

In addition to the dose modification and hyperglycemia treatment guidelines in Table 4-1:

- Under the supervision of an endocrinologist, an insulin regimen should be initiated according to institutional standard of care or the Treat-To-Target Algorithm for Lantus®(Riddle, Rosenstock, and Gerich 2003).
- For any hyperglycemia ≥ grade 1, the patient should continue to follow dietary guidelines provided by the American Diabetes Association (American Diabetes Association 2004).
- For each patient, a maximum of 2 dose reductions will be allowed after which the patient should be discontinued from the study. In addition, a patient must discontinue treatment with buparlisib, if after treatment is resumed at a lower dose, hyperglycemia recurs at a worse severity.
- For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated in that patient during future treatment cycles with buparlisib.
- Based upon the results of preliminary clinical data and actual laboratory values (e.g., glucose, insulin) generated, the treatment recommendations for study drug induced hyperglycemia may be modified as needed.

4.1.2.5 Cardiac events

Cardiac safety studies, conducted in vitro and in vivo, did not indicate a prominent electrophysiological risk. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, observed in two dog telemetry studies. As a precaution in the first-in-man study with buparlisib no patients with a severe or unstable cardiac disease or cardiac disease requiring continuous treatment, and no patients with uncontrolled hypertension will be enrolled in early clinical studies. In addition, HER2 positive patients will be assessed for cardiac diseases before start of treatment, while HER2 positive patients enrolled in the trial will undergo regular cardiac monitoring throughout the conduct of the trial. For the treatment of acute cardiac events occurring under buparlisib treatment investigators are advised to adhere to the protocol guidelines. Vital signs, including pulse rate and blood pressure, will be closely followed during the early clinical studies.

4.1.2.5.1 Management of Cardiac events

At the screening visit a 12-lead electrocardiogram (ECG), will be performed to assess eligibility. Repeat ECGs will be performed at screening and as clinically indicated.

At the screening visit an echocardiogram or MUGA (ECHO/MUGA) for HER2 positive patients only will be performed to assess eligibility. Cardiac imaging will be repeated at 4 months and then every 4 months thereafter for HER2 positive patients only. End of Treatment ECHO/MUGA not required. There is window of +/- 7 business days for an ECHO/MUGA. Any delay within this window is NOT a deviation as per the visit schedule (Table 4-12).

4.1.2.5.2 Management of Pneumonitis

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

In ongoing clinical trials with buparlisib in the single agent setting two cases of Pneumonitis occurred. In the study BKM120X2101 one patient experienced Pneumonitis (grade 2) eight weeks after the first dose of buparlisib at 100mg which resolved in 7 days after antibiotic therapy and discontinuation of the study treatment due to fatigue. In the Japanese study BKM120X1101 one case of Pneumonitis occurred in a patient (given 100 mg) one month after the start of study medication with buparlisib. The patient experienced Pneumonitis with fatal outcome which was concomitant to progression of underlying malignancy including the progression of existing and the appearance of new lesions in combination with increasing pleural effusion (please see current Buparlisib Investigators Brochure for more details).

All patients participating in clinical trials administering buparlisib will be routinely asked about the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function test should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed Pneumonitis. In case of a documented Pneumonitis, the guidelines (including the dose modifications) in Table 4-5 should be followed. Consultation with a pulmonologist is highly recommended for any Pneumonitis case identified during the study.

Table 4-5 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 until return to within normal limits.	No specific therapy is required	Administer 100% of buparlisib dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce buparlisib dose by 1 dose level (see Table 4-0) until recovery to $\leq$ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to $\leq$ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with buparlisib until recovery to $\leq$ Grade 1. May restart study treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with buparlisib.

4.1.2.5.3 Management of Liver Toxicities

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

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

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

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

4.1.3 Criteria for capecitabine dose modification

A capecitabine dose reduction will be administered as described in Table 4-6. For grade ≥2 capecitabine-related toxicities (hand/foot syndrome, mucositis, diarrhea), capecitabine treatment should be delayed until resolution to grade 0 or 1, then resumed at the next lower dose level. For each patient, a maximum of 2 dose reductions will be allowed after which the patient will be discontinued from treatment with capecitabine. The dose of capecitabine does not need to be reduced for toxicities that the physician believes are due to buparlisib. Initial dosing, as well as delays and/or dose reductions will be recorded on the patient diary and the EDC.

Table 4-6 Dose modification steps for Capecitabine

Capecitabine dose levels	**Dose* and schedule**
Starting dose level	1000** mg/m^2 BID days 1-14 of 21 day cycle
Dose level -1	750** mg/m^2 BID days 1-14 of 21 day cycle
Dose level -2	750** mg/m^2 mg BID days 1-7 of 14 day cycle
*** Dose reduction should be based on worst preceding toxicity** **** Rounded down to nearest 500 mg pill**	

4.1.4 Trastuzumab – Cardiac Monitoring and Cardiomyopathy Management Guidelines

Trastuzumab dose modifications will be per physician's discretion and standard of care.

Left ventricular ejection fraction (LVEF) should be assessed prior to initiation of trastuzumab and at regular intervals during treatment. Withhold trastuzumab and capecitabine/buparlisib dosing for at least 4 weeks for either of the following:

- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Trastuzumab plus capecitabine/buparlisib may be resumed if, within 4−8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤ 15%. Permanently discontinue trastuzumab and capecitabine/buparlisib for a persistent (> 8 weeks) LVEF decline or for suspension of trastuzumab dosing on more than 3 occasions for cardiomyopathy. If trastuzumab is stopped for toxicity other than cardiac toxicity, capecitabine/buparlisib may be continued until PD or intolerable toxicity.

4.1.5 Reasons off treatment

Patients will be taken off treatment if any of the following occur:

1. Disease progression
2. Intolerable toxicity

   Note: If any patient goes off study treatment due to any adverse event, regardless of grade, the reason for off treatment will be documented as an "Adverse event" in eDC; the toxicity (regardless of grade) must be documented in the toxicity section of eDC with the action code entered that is appropriate for discontinuation of study treatment.
3. Physician decision. An intercurrent illness, which would in the judgment of the Investigator affect assessments of clinical status to a significant degree or require discontinuation of study treatment, non protocol therapy, or non-compliance.
4. Becomes pregnant
5. Patient refuses to continue treatment (patient will continue to be followed for survival)
6. Normal completion of treatment portion of the protocol

The date of and reason for discontinuation must be noted on the Change of Status page of the eCRF. Every effort should be made to complete the appropriate assessments.

4.1.6 Reasons for taking patients "off study"

Patients will be considered "off study" if any of the following occur:

1. Termination of the study by Delta and/or the Sponsor decision

2. Withdrawal of consent (patient will not be contacted and no further information will be collected)

   Note: If the patient withdraws consent, then no additional data will be collected without his/her explicit consent; all data collected prior to withdrawal of consent may be used in the data analysis. The only exception to the collection of data after withdrawal of consent is collection of **date of death** and cause of death (if available) when the endpoint of the study is mortality.

3. Lost to follow-up (3 attempts should be documented in the patient's source document before the site considers the patient as LFU.)

4. Death

5. Discontinuation of the patient when determined by the Study Investigator that continuation of the patient on study is no longer in the best medical interest of the patient.

The appropriate information must be completed on the Change of Status page of the eCRF.

4.2 Treatments

4.2.1 Study treatment administration

Buparlisib

The study drug buparlisib will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Buparlisib will be administered on a continuous once daily dosing schedule. Patients should be instructed to take the dose of buparlisib daily in the morning, one hour after a light breakfast (morning meal) at approximately the same time each day. Buparlisib should be taken with an 8 oz glass of water consumed over as short a time as possible. Patients should swallow the capsules whole and not chew them. Patients should not crush the capsule. Patients should continue to fast for 2 hours after the administration of each buparlisib dose.

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

If the patient forgets to take her/his dose until AFTER 6:00 PM, then the dose should be withheld that day and buparlisib should be restarted the following day.

Patients must avoid consumption of St. John's Wort, Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study medication and during the entire study treatment period due to potential CYP3A4 interaction with the study medication. Patients must avoid concomitant intake of strong and moderate CYP3A4/5 inhibitors and inducers. See Table 4-8. Orange juice is allowed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. If a patient requires a buparlisib dose delay of > 21 days from the previous dose, the patient must be discontinued from treatment completely and will only require a 28 day follow up visit for study completion.

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

Capecitabine

Capecitabine will be supplied according to local practice. Capecitabine is commercially available as film-coated tablets (500 mg) for oral administration. Capecitabine will be dosed 1000 mg/m^2 PO BID 14 days on/7 days off (dose rounded down to nearest 500 mg pill). Capecitabine will be stored in accordance with labeled storage conditions at 25°C (77°F), with excursions permitted from 15 to 30°C (59 to 86°F) [controlled room temperature].

The appropriate number of capecitabine tablets (500 mg) to make up a 14-day course will be prescribed to subjects to be self-administered at home. Capecitabine will not be supplied on this trial but will be obtained by prescription as a standard of care drug.

Treatment will be administered on an outpatient basis. Tablets should be taken with water, at approximately 12-hour intervals, within 30 minutes after breakfast and dinner. As stated in the labeling for Xeloda® (capecitabine), care should be exercised when capecitabine is coadministered with CYP2C9 substrates.

Full details for capecitabine can be found in its Package Insert.

Trastuzumab

Patients with HER2+ MBC will receive trastuzumab 6 mg/kg IV every 3 weeks along with capecitabine and buparlisib as detailed above. Patients who require a loading disease may receive 8 mg/kg IV trastuzumab for their first dose. Trastuzumab dose modifications will be per physician's discretion and standard of care.

4.2.2 Dosing regimen

All eligible patients will receive buparlisib 100 mg administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in combination with capecitabine 1000 mg/m^2 PO BID Days 1-14 of a 21 day cycle. (Table 4-7) Patients with HER2+ MBC will also receive trastuzumab every 3 weeks. Patients who require a loading disease may

receive 8mg/kg IV trastuzumab for their first dose. Patients will then receive trastuzumab 6mg/kg IV every 3 weeks along with capecitabine and buparlisib.

A complete cycle of treatment is defined as 21 days of once daily continuous treatment of buparlisib in combination with capecitabine twice daily on Days 1-14.

The suggested timing is for patients to eat a light breakfast followed by the morning dose of capecitabine within 30 minutes. Buparlisib should be taken 1 hour after the light breakfast, after which the patient should fast for 2 hours (water allowed). The evening dose of capecitabine should be taken within 30 minutes following dinner. An oral medication diary will be provided (Appendix 5).

Table 4-7 Buparlisib and Capecitabine (and Trastuzumab for HER2+ MBC) Dose and treatment schedule

Study drugs	Pharmaceutical form and route of administration	Dose[b]	Frequency and/or Regimen
Buparlisib	**Capsules for oral use**	**100 mg (2x 50mg capsules[a])**	**Daily**
Capecitabine	**Film-coated tablets for oral use**	**1000 mg/m^2 BID[c]**	**Days 1-14 followed by 7 days off**
Trastuzumab	**IV**	**6 mg/kg[d]**	**Every 3 weeks**

[a] In case of patient supply difficulties, any combination of buparlisib 50 mg or 10 mg capsules may be taken to constitute a dose of 100 mg/day (or dose reduction level).

[b] Dose reduction levels for buparlisib will be administered accordingly. For example, buparlisib 80 mg should preferentially be administered as 1x50mg size capsule, and 3x10 mg size capsule.

[c] Capecitabine dose should be rounded down to the nearest 500 mg pill.

[d] A loading dose of 8 mg/kg of trastuzumab may be administered with the first cycle if required.

4.2.3 Concomitant therapy

All medications taken within 4 weeks prior to the administration of buparlisib and all concomitant therapy administration during the study with reasons for therapy should be recorded. All prior chemotherapy; biologic, immunologic or radiation therapy; and surgery within 4 weeks prior to the administration of study drug, will be recorded.

Patients on chronic medications that can be given concomitantly with buparlisib should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study

drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions described in Section 4.2.3.1.

4.2.3.1 Drugs that are prohibited

- Other investigational therapies must not be used while the patient is on the study.
- Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study. If such agents are required for a patient then the patient must be discontinued from the study.
- In *vitro* metabolism studies suggest that oxidative metabolism of buparlisib is predominantly mediated by CYP3A4 (fm>0.9), with only minor contributions of CYP1A1. As buparlisib is a sensitive CYP3A4 substrate, co-administration of buparlisib with any strong and moderate CYP3A4 inhibitors and CYP3A4 inducers is prohibited. Refer to Table 4-8 for a list of prohibited drugs. Please note this list may not be comprehensive.
- Based on in vitro studies, co-administration of buparlisib with CYP3A4 inducers is predicted to decrease the systemic exposure to buparlisib, thereby increasing the risk of exposing the patient to subtherapeutic drug levels. Refer to Table 4-8 for a list of prohibited CYP3A inducers. Please note that this list may not be comprehensive. **Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-derivative anticoagulants are not permitted.**
- If a patient requires the concomitant use of any medication included in Table 4-9 entitled “List of Prohibited QT prolonging drugs” (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a risk of causing Torsades des de Pointes), study treatment administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to St. John’s wort, Kava, ephedra (ma huang), ginko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
- Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective in this study.

Table 4-8 List of prohibited CYP3A Inhibitors and Inducers

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

This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase buparlisib AUC > 5-fold, and moderate inhibitors are predicted to increase buparlisib AUC ≥ 2-fold but < 5-fold.
This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche et al. 2008).

Table 4-9 List of prohibited QT prolonging drugs

All QT-prolonging drugs listed in Table 4-9 are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 4-10 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

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 sibstrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

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

4.2.3.1 Drugs to be used with caution

Preliminary in vitro metabolism studies suggest that buparlisib is a weak, reversible inhibitor of CYP3A4/5 (Ki=13.6 μM, [I]/Ki= 0.4 where [I] is the average C_{max} at steady-state following 100 mg daily dose) and a weak reversible inhibitor of CYP2C8/2C9/2C19 (IC_{50}=34 μM, [I]/IC_{50}=0.15). Note: that with the data available, we are not able to confirm whether such interactions will occur in patients. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Patients receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate. Please refer to Table 4-11 for a list of CYP450 substrates and carefully consider their co-administration with buparlisib.

Particular caution is advised when buparlisib is co-administered with:

- Drugs which are substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index.
- Oral anti-diabetic drugs which are metabolized by CYP2C8 or CYP2C9 can possibly result in hypoglycemia. Patients who develop diabetes mellitus during the study should be treated according to the American Diabetes Association guidance. It is recommended that treatment start with metformin.
- If a patient, after study enrollment, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for Torsade de Pointes then the investigators, at their discretion, may co-administer such medications. Patients receiving such medications must be monitored. Refer to Table 4-10 for a list of QT prolonging medications to be used with caution.

  Note: please refer also to Table 4-9 for a list of **prohibited** QT prolonging medications.
- Please refer to Table 4-11 for a list of CYP450 substrates and carefully consider their co-administration with buparlisib.
- Concomitant treatment with corticosteroids and buparlisib should be avoided, whenever possible, during this study. A short duration (< 2 weeks) of systemic corticosteroids is allowed (e.g. for chronic obstructive pulmonary disease, or as an anti-emetic). Chronic dosing of corticosteroids is known to induce CYP3A enzymes, thereby increasing the risk or reducing buparlisib overall exposure to sub-therapeutic levels. Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed.

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

Drug	QT risk	Comment
Alfuzosin	possible risk for Torsades de Pointes	
Amantadine	possible risk for Torsades de Pointes	
Amitriptyline	conditional risk for Torsades de Pointes	
Azithromycin	possible risk for Torsades de Pointes	
Chloral hydrate	possible risk for Torsades de Pointes	
Citalopram	conditional risk for Torsades de Pointes	
Clomipramine	conditional risk for Torsades de Pointes	
Clozapine	possible risk for Torsades de Pointes	
Desipramine	conditional risk for Torsades de Pointes	
Diphenhydramine	conditional risk for Torsades de Pointes	
Dolasetron	possible risk for Torsades de Pointes	
Doxepin	conditional risk for Torsades de Pointes	
Dronedarone	possible risk for Torsades de Pointes	
Felbamate	possible risk for Torsades de Pointes	
Flecainide	possible risk for Torsades de Pointes	
Fluoxetine	conditional risk for Torsades de Pointes	
Foscarnet	possible risk for Torsades de Pointes	
Fosphenytoin	possible risk for Torsades de Pointes	
Galantamine	conditional risk for Torsades de Pointes	
Gatifloxacin	possible risk for Torsades de Pointes	
Gemifloxacin	possible risk for Torsades de Pointes	
Granisetron	possible risk for Torsades de Pointes	
Imipramine	conditional risk for Torsades de Pointes	
Indapamide	possible risk for Torsades de Pointes	
Isradipine	possible risk for Torsades de Pointes	
Levofloxacin	possible risk for Torsades de Pointes	
Lithium	possible risk for Torsades de Pointes	
Mexiletine	conditional risk for Torsades de Pointes	
Moexipril/HCTZ	possible risk for Torsades de Pointes	
Moxifloxacin	possible risk for Torsades de Pointes	
Nicardipine	possible risk for Torsades de Pointes	
Nortriptyline	conditional risk for Torsades de Pointes	
Octreotide	possible risk for Torsades de Pointes	
Ofloxacin	possible risk for Torsades de Pointes	
Ondansetron	possible risk for Torsades de Pointes	
Oxytocin	possible risk for Torsades de Pointes	
Paliperidone	possible risk for Torsades de Pointes	
Paroxetine	conditional risk for Torsades de Pointes	
Perflutren lipid	possible risk for Torsades de Pointes	

Drug	QT risk	Comment
microspheres		
Protriptyline	conditional risk for Torsades de Pointes	
Ranolazine	possible risk for Torsades de Pointes	
Risperidone	possible risk for Torsades de Pointes	
Roxithromycin*	possible risk for Torsades de Pointes	*not available in the United States
Sertindole	possible risk for Torsades de Pointes	
Sertraline	conditional risk for Torsades de Pointes	
Solifenacin	conditional risk for Torsades de Pointes	
Tizanidine	possible risk for Torsades de Pointes	
Trazodone	conditional risk for Torsades de Pointes	
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes	
Trimipramine	conditional risk for Torsades de Pointes	
Venlafaxine	possible risk for Torsades de Pointes	
Ziprasidone	possible risk for Torsades de Pointes	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Table 4-11 List of CYP450 Substrates to be used with caution

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

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

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

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

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

4.2.3.2 Bisphosphonates and denosumab

The use of bisphosphonates or denosumab is allowed provided patients have been on stable doses for at least 4 weeks prior to treatment start. Stable dose and same brand should be maintained during the treatment period. Patients requiring initiation of bisphosphonates or denosumab treatment during the course of the study should be discontinued due to progressive disease unless disease progression can be completely ruled out and is clearly documented in the patients' source documentation.

4.2.3.3 Palliative radiotherapy

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required provided no lung tissue will be included in the radiation portal, and no or minimal GI tissue will be included in the radiation portal. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. No dose modification of study treatment is needed during palliative radiotherapy.

4.3 Visit Schedule and Assessments

4.3.1 Visit schedule

Table 4-12 lists all of the assessments and indicates with an "X" when the visits are to be performed. All data obtained from these assessments must be recorded in the patient's source documentation.

Sections 4.3.2 - 4.3.13 lists all of the assessments required for the collection plan for Imaging, Clinical Laboratory parameters, and PHQ-9/GAD-7 patient self-reported questionnaires. The outlined schedule should be adhered to for all analyses. In general, where possible, every effort must be made to follow the schedule outlined in Table 4-12 and in subsequent tables.

Table 4-12 Schedule of Events

Schedule of Events								
	Screening phase	Treatment phase (cycle is defined as 21 days ± 3 business days)					Post-treatment follow up phase (± 7 business days)	Survival phase (± 7 business days)
Cycle		Cycle 1	Cycle 2	Cycle 3	Preceding cycles (Day 1 of Each Cycle)	End of treatment (± 7 business days)	Endpoint follow up (safety and efficacy follow up)	Survival follow up (every 2 months and more frequent if required)
Days	-28 to -1	1	1	1	1			
Obtain study Informed Consent and HIPAA	X							
Collect and send tumor biopsy (archival paraffin blocks/slides or fresh biopsy)	X (Day -28 to -1)							
Demography	X							
Inclusion/exclusion criteria	X							
ER and PgR status	X							
HER2 status	X							
Relevant medical history/current medical conditions (to include GPA components)	X							
Diagnosis and extent of cancer	X							
Prior antineoplastic therapy (surgery, medication, radiotherapy)	X							
Physical examination	X	X*	X	X	X	X		
Performance status (ECOG)	X	X*	X	X	X	X		

Schedule of Events								
	Screening phase	**Treatment phase (cycle is defined as 21 days ± 3 business days)**					**Post-treatment follow up phase (± 7 business days)**	**Survival phase (± 7 business days)**
Cycle		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Preceding cycles (Day 1 of Each Cycle)**	**End of treatment (± 7 business days)**	**Endpoint follow up (safety and efficacy follow up)**	**Survival follow up (every 2 months and more frequent if required)**
Days	**-28 to -1**	**1**	**1**	**1**	**1**			
Height	**X**							
Weight	**X**	**X***	**X**	**X**	**X**	**X**		
Vital signs	**X**	**X***	**X**	**X**	**X**	**X**		
Hematology	**X**	**X***	**X**	**X**	**X**	**X**		
Biochemistry (CMP) [3]	**X**	**X***	**X**	**X**	**X**	**X**		
Urinalysis	**X**					**X**		
Amylase and Lipase	**X**	**Repeat every 8 weeks**						
Fasting plasma glucose[4]	**X**	**X***	**X**	**X**	**X**	**X**		
Glycosylated Hemoglobin (HbA1c)	**X**	**as clinically indicated**				**X**		
Coagulation PT or INR,PTT[5]	**X**	**Repeat at week 4, then every 8 weeks thereafter**						
Serum/Urine Pregnancy Test	**X**	**As clinically indicated[1]**						
12-lead ECG/EKG	**X**	**As clinically indicated**						
ECHO/MUGA HER2+ patients Only	**X**	**Cardiac imaging to repeat every 4 months for HER2+ patients on Herceptin Only**						
Brain MRI	**X**	**8 weeks after initiation of treatment, then every 8 weeks thereafter (Assessments window is ± 7 business days.)**				**X**	**Per Standard of Care for patients off all study treatment**	

Schedule of Events								
	Screening phase	**Treatment phase (cycle is defined as 21 days ± 3 business days)**					**Post-treatment follow up phase (± 7 business days)**	**Survival phase (± 7 business days)**
Cycle		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Preceding cycles (Day 1 of Each Cycle)**	**End of treatment (± 7 business days)**	**Endpoint follow up (safety and efficacy follow up)**	**Survival follow up (every 2 months and more frequent if required)**
Days	**-28 to -1**	**1**	**1**	**1**	**1**			
CT or MRI (Chest, abdomen)	**X**	**8 weeks after initiation of treatment, then every 8 weeks thereafter (Assessments window is ± 7 business days.)**				**X**	**Per Standard of Care for patients off all study treatment**	
CT or MRI for any site of measurable disease (excluding bone)	**X[6]**	**If lesion at screening, 8 weeks after initiation of treatment, then every 8 weeks thereafter (Assessments window is ± 7 business days.)**				**X (if lesion at screening)**	**Per Standard of Care for patients off all study treatment**	
Bone scan	**X**	**If bone lesion at screening, 8 weeks after initiation of treatment, then every 8 weeks thereafter (Assessments window is ± 7 business days.)**				**As clinically indicated**	**As clinically indicated**	
Skin – color photography	**Only if skin lesions at screening**	**If skin lesions at screening, 8 weeks after initiation of treatment, then every 8 weeks thereafter (Assessments window is ± 7 business days.)**				**Mandated only if skin lesions at screening**	**Per Standard of Care for patients off all study treatment**	
RECIST version 1.1	**X**	**Performed every 8 weeks after initiation of treatment, thereafter (Assessments window is ± 7 business days.) Tumor response will be assessed locally according to Response Evaluation Criteria in Solid Tumors**				**X**	**As clinically indicated**	

Schedule of Events								
	Screening phase	**Treatment phase (cycle is defined as 21 days ± 3 business days)**					**Post-treatment follow up phase (± 7 business days)**	**Survival phase (± 7 business days)**
Cycle		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Preceding cycles (Day 1 of Each Cycle)**	**End of treatment (± 7 business days)**	**Endpoint follow up (safety and efficacy follow up)**	**Survival follow up (every 2 months and more frequent if required)**
Days	**-28 to -1**	**1**	**1**	**1**	**1**			
MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT) Assessment	**X**	**8 weeks after initiation of treatment, then every 8 weeks thereafter (Window ± 3 business days)**				**X**		
Neuro-psychiatric assessment (self rating mood questionnaire)[2]	**X**	**X**	**X**	**X**	**X**	**X**		
Neurologic assessment	**X**	**8 weeks after initiation of treatment, then every 8 weeks thereafter (Assessments window is ± 7 business days.)**				**X**		
Prior/concomitant medications	**X**	**Continuous**					**Up to 30 days after last dose of treatment**	
Adverse events	**X**	**Continuous**					**Up to 30 days after last dose of treatment**	
Antineoplastic therapies since discontinuation of study treatment							**X**	**X**
Buparlisib administration		**Daily starting from Cycle 1 Day 1**						
Capecitabine administration		**Daily days 1-14**	**Daily days 1-14**	**Daily days 1-14**	**Daily days 1-14**			
Trastuzumab administration (HER2+ MBC		**Every 3 weeks**						
Patient diary		**Continuous**						

Schedule of Events

	Screening phase	Treatment phase (cycle is defined as 21 days ± 3 business days)					Post-treatment follow up phase (± 7 business days)	Survival phase (± 7 business days)
Cycle		**Cycle 1**	**Cycle 2**	**Cycle 3**	**Preceding cycles (Day 1 of Each Cycle)**	**End of treatment (± 7 business days)**	**Endpoint follow up (safety and efficacy follow up)**	**Survival follow up (every 2 months and more frequent if required)**
Days	**-28 to -1**	**1**	**1**	**1**	**1**			
Survival follow up								**X**

Note: Cycle 1 only, the baseline values for those assessments (laboratory, physical examination, performance status and vital signs) that are to be done prior to every cycle may be used for Cycle 1 assessments as long as they are completed within 2 weeks prior to the patient receiving their first dose of study drug. If more than 2 weeks have elapsed since the baseline assessment, the assessment must be repeated. Assessments need to be put in the order in which they appear in eCRF. Treatment must begin within 5 working days after patient registration to the study, not including weekends or holidays.

[1] Serum/urine pregnancy test (β-HCG) is required for all women of child-bearing potential at screening, within 3 business days prior to the first dose of buparlisib. And as clinically indicated thereafter.
[2] Questionnaires PHQ-9 and GAD-7 will be completed at each visit. Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study.
[3] Biochemistry (CMP) includes K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, amylase, GGT, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, urea or BUN, albumin, and total protein, to be obtained on the first day of each cycle. Lab assessments may be performed up within 3 business days prior to the scheduled visit, but all other draws should occur within 24 hours of the intended visit.
[4] Patients must be fasting overnight for at least 8 hours. Additional measurements may be performed as clinically indicated.
[5] Coagulation – PT, or INR, PTT, and C1D1 assessments may be performed up to 72 hours prior to the scheduled visit. Additional assessments will be performed on Day 1 of Cycle 2 (within 3 business days prior to dosing) and repeated every other cycle. A repeat coagulation profile panel is required at the time of study treatment discontinuation. Patient entering the study while receiving anti-coagulation therapy or those who have the initiation of an anti-coagulation therapy should have their coagulation test performed on a weekly basis.
[6] Mandated if suspected lesion at screening.

4.3.2 Efficacy assessments

Tumor response will be assessed locally according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (Appendix 4). The local investigator's assessment will be used for all endpoint analyses and for treatment decision making with a +/- 7 day window. Any delay within this window is not a deviation.

Table 4-13 Efficacy Assessments

Procedure	Screening: Day−14 (up to -21) to Day -1	Treatment phase*	End of treatment*	Post-treatment follow-up phase: Efficacy follow-up*
CT or MRI (Chest, Abdomen)	Mandated	8 weeks after initiation of treatment and then every 8 weeks **(Assessments window is ± 7 business days.)**	Mandated	Per Standard of Care for patients off all study treatment
CT or MRI for any site of measurable disease (excluding bone)	Mandated if suspected lesion at screening	If lesion at screening: 8 weeks after initiation of treatment and then every 8 weeks **(Assessments window is ± 7 business days.)**	Mandated if lesion at screening	Per Standard of Care for patients off all study treatment
Brain MRI	Mandated	8 weeks after initiation of treatment and then every 8 weeks **(Assessments window is ± 7 business days.)**	Mandated	Per Standard of Care for patients off all study treatment
Bone scan	Mandated	If bone lesions at screening 8 weeks after initiation of treatment and then every 8 weeks **(Assessments window is ± 7 business days.)**	As clinically indicated	As clinically indicated
Skin - color Photography	Mandated if skin lesions at screening	If skin lesions at screening 8 weeks after initiation of treatment and then every 8 weeks **(Assessments window is ± 7 business days.)**	Mandated if skin lesions at screening	**Per Standard of Care for patients off all study treatment**
*Tumor evaluation at EOT is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment and for patients whose previous tumor assessment did not demonstrate PD and was done at least 6 weeks (± 4 days) prior to end of treatment visit. Tumor assessments are to be done every 8 weeks after initiation of treatment.				

Neurologic Assessment

Neurologic assessment should be performed at baseline, every 8 weeks following initiation of study treatment, and at the end of treatment visit. Assessment should include cranial nerves exam, and motor and sensory exam. In addition, patients should be assessed both for ability to walk and for balance using the following criteria:

- Normal
- Mildly impaired
- Moderately impaired
- Severely impaired (in wheelchair)

Exploratory biomarker analysis – formalin-fixed Paraffin-embedded (FFPE) tumor samples

Tumor tissue (formalin fixed new biopsy or archival) is required, and will be stored for future analysis of markers shown to be closely associated with the PI3K pathway, including but not limited to PTEN and INPP4B. One tumor block (preferred) or a minimum of 15 paraffin-dipped unstained slides is required. Fresh biopsy tissue from a resected brain metastasis is preferred but an archival sample from the primary breast cancer may be submitted.

Since the archival samples may not be located at the institution where the original diagnosis was rendered, the investigational sites will be responsible for locating them and preparing the unstained slides (or having them prepared), if necessary.

For all tumor samples, the sample collection information must be captured on the relevant eCRF page(s) and laboratory requisition form(s).

Tumor samples will be sent to designated lab (check CTI) for analysis. See Collection of Shipping Information provided by sponsor for more detailed instruction on sample preparation and submission information.

4.3.3 Safety assessments

Safety assessments will consist of the following: monitoring and recording of all adverse events and serious adverse events; the regular monitoring of hematology, blood chemistry, urinalysis; regular measurement of vital signs, oxygen saturation, physical examination, including weight; and performance status.

These assessments should be performed periodically throughout the study, except for adverse events that will be evaluated continuously.

All patients who receive at least one dose of study drug will be evaluated for safety. Toxicities will be graded and reported according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03 (Appendix 3). Incidence and type of AEs will be tabulated and summarized using descriptive statistics.

4.3.4 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

4.3.5 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation given during any phase of the trial.

If it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (ie, any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded at baseline. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

4.3.6 Serious adverse events

Information about all serious adverse events will be collected and recorded on the FDA MedWatch 3500a form. To ensure patient safety, each serious adverse event must also be reported to Delta within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom, or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen

- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

For instructions about returning Serious Adverse Event Report Forms to Delta refer to the protocol section entitled Instructions for Rapid Notification of Serious Adverse Events (Section 4.3.7).

4.3.7 Instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the IRB and the sponsor, (Delta Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)). Serious adverse events should also be reported to the FDA and IRB in accordance with regulations and IRB policy.

The investigator must complete the FDA MedWatch 3500A form and Delta SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Delta SAE coversheet by Fax to 1.888.299.4565 within 24 hours to the local Delta Drug Safety & Epidemiology (DS&E) Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Delta DS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Delta SAE coversheet, and the fax confirmation sheet must be kept with the electronic case report forms (eCRF) at the study site.

In addition, all SAEs will be reported by telephone to the Delta Central Safety Department as soon as study personnel become aware of the SAE. The SAEs should be reported by facsimile within 24 hrs to the Delta Central Safety Department. The site will supply as much information as is available at the time of the initial Fax to the Delta Central Safety Department (study number, subject initials, subject study number, event), during both business and nonbusiness hours, to:

Delta Clinical Research Safety Department
10101 Woodloch Forest

The Woodlands, TX 77380
SAE Hotline: (281) 863-6503
Safety Fax: (877) 571-8934

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form, Delta SAE coversheet, and fax confirmation sheet must be retained.

Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

Adverse events will be recorded for the duration of a patient's study treatment. All AEs, regardless of causal relationship, are to be recorded in the source documentation. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

All AEs will be graded and reported according to the NCI Common Toxicity Criteria (version 4.03). The relationship of each event to the study drug will be assessed by the Investigator and recorded on the eCRF. Additional information about each event, such as treatment required, whether or not the study drug had to be discontinued, and eventual outcome will also be recorded on the eCRF.

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. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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)..

4.3.7.1 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is 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 Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of buparlisib to any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

4.3.8 Laboratory evaluations

Pregnancy Test

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

Hematology

Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell (RBCs), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count to be obtained on the first day of each cycle. Lab assessments may be performed within 3 business days prior to the scheduled visit.

Coagulation Profile

The coagulation profile includes prothrombin time or INR, and activated partial thromboplastin time to be drawn within 24 hours of the intended visit.

Serum chemistry

Biochemistry includes the K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, GGT, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), bicarbonate, glucose, urea or BUN, albumin, and total protein to be obtained on the first day of each cycle. Lab assessments may be performed within 3 business days prior to the scheduled visit.

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

4.3.9 Vital signs

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

4.3.10 Physical examination

Physical examination will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

4.3.11 Neuropsychiatric assessments

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

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

Additional assessments may be done according to the clinical judgment of the Investigator. Symptomatic patients (≥ CTCAE grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study. The nurse or the CRC will provide the patient with the instruments and the instructions on how to complete the questionnaires, as well as how to determine the scores. See Appendices 5 and 6 for questionnaires.

4.3.12 ECG/EKG –ECHO/MUGA

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

An echocardiogram (ECHO) or MUGA will be performed to assess eligibility for HER2 positive patients only. ECHO/MUGA will be repeated at 4 month intervals thereafter for HER2 positive patients only. There is window of +/- 7 business days for an ECHO/MUGA. Any delay within this window is NOT a deviation as per the visit schedule (Table 4-12).

4.3.13 Performance status

Performance status will be assessed at screening and per the visit schedule. The ECOG Performance Status Scale will be used. (See Appendix 2)

4.3.14 Disease-related symptom assessment

Disease-related symptoms will be assessed at screening, every 8 weeks during treatment, and at the end of treatment. The MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT) module will be used (see Appendix 6).

4.3.15 Drug levels and pharmacokinetic assessments

No pharmacokinetic assessments will be performed.

5 Data management

5.1 Data collection

Investigators must record the information required by the protocol.

6 Statistical methods

6.1 Populations for analysis

6.1.1 Analysis populations

Intent-To-Treat (ITT) Population: Includes all patients registered on the study (eligible and ineligible). This ITT population will be included in overall patient listings, in summary tables of patient demographics and baseline disease characteristics, and also in the list of treatment discontinuations after enrollment. This population will also be used for analyses of overall survival (OS) and time to progression (TTP).

Evaluable Population: Includes all eligible patients who meet the protocol-specified efficacy analyses requirements and who have received at least 1 dose of study drug. This population will comprise those with a CR, PR, SD, PD, or NE response.

Safety Population: Includes all patients (eligible and ineligible) who receive at least 1 dose of study drug. This safety population will also be used for the summaries and analysis of all safety parameters (drug exposure, tables of adverse events information, including serious adverse events, etc).

6.1.2 Patient characteristics

All patients entered in the study will be accounted for in the summation. Patient demographics and baseline characteristics such as age, race, sex, ECOG PS, and ER/PR/HER2 status will be described. Disease stage and histology at baseline, medical history, and prior treatment, including WBRT and SRS, will also be summarized. Mean, standard deviation, median, minimum and maximum values will be presented for continuous

variables, and frequency tables showing numbers and percentages will be presented for categorical variables.

6.1.3 Patient disposition

Patient disposition including the number of patients enrolled, completed, and discontinued from the study will be summarized by numbers and percentages. The reasons for discontinuation will also be summarized in the same manner.

6.2 Hypothesis and endpoints

This is an open-label, one arm, multicenter phase 2 trial of buparlisib plus capecitabine in breast cancer patients with brain metastases that have been previously treated with WBRT or SRS or both.

CBR will be the primary endpoint for this study and is defined as objective response (CR + PR) plus stable disease ≥24 weeks. ORR, OS, TTP, safety, time to deterioration of neurologic function, changes in symptom occurrence, and a correlation between PI3K pathway-related biomarkers and clinical response are the secondary endpoints and will also be followed and described in this study.

6.3 Sample size and projected study duration

14 patients will be entered into each of 3 patient cohorts: ER+/HER2-, HER2+, and triple negative disease. If the true CBR is 30% in any of the 3 cohorts, observing 3 of 10 patients achieving clinical benefit will yield a 90% confidence interval for CBR from 6-54%. If the true CBR is 15% in any of the 3 cohorts, observing 3 of 10 patients achieving clinical benefit will yield a 90% confidence interval for CBR from 1-34%. If 3 or more of the 14 patients . in any cohort has clinical benefit from the combination, we will discuss with Novartis the potential of expanding that cohort to enroll addition patients. With an estimated accrual rate of 3 patients per month, a follow-up of 12 months, and an additional 6 months for data lock and report development, the total time to the initial release of findings would be around 2.5 years.

6.4 Statistical methods

6.4.1 Primary efficacy analysis

CBR in the patients following WBRT or SRS or both will be the primary endpoint and is calculated as the total number of responders (CR or PR) plus stable disease greater than or equal to 24 weeks (CR + PR + SD ≥ 24 weeks) divided by the total number of evaluable patients. .

6.4.2 Secondary efficacy analysis

The incidence of responses of CR, PR, ORR, SD, PD, and NE (using RECIST 1.1) with 95% CI will be tabulated and summarized using descriptive statistics by the exact-binomial method in the evaluable population. Time to response and duration of response will be calculated.

OS will be measured from the date of registration to the date of death for patients who die. If a patient is still alive or is lost to follow up, the patient will be censored at the last contact date. OS will be estimated using the Kaplan-Meier method and Breast-GPA-estimated method in the ITT population. Number of Patients who died, and causes of death will be reported. The Graded Prognostic Assessment (GPA) will be calculated by Karnofsky PS, subtype of breast cancer, and age group (Appendix 1). TTP will be calculated from the date of registration to the date of the first documented progression or the date of death due to disease progression, whichever comes first. If the patient did not progress or die due to disease progression, the patient will be censored at the date of last contact. TTP will be summarized using the Kaplan-Meier method in the ITT population.

Toxicity profiles will be tabulated in the safety population. Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (version 4.0). Subjects enrolled in this study will be carefully monitored during the entire treatment phase and will be followed as is appropriate. Incidence and type of adverse events, including serious adverse events, will be tabulated. Adverse events that occur >30 days after the administration of last treatment will not be reported. Median cycles received, median drug delivered per dose and cumulative doses, dose compliances, dose modifications, and reasons of the dose modifications will be summarized.

Time to deterioration of neurologic function will be estimated using Kaplan-Meier method in safety population. Results of the PHQ-9 Depression Scale will be tabulated, as well as the MDASI-BT questionnaire results.

In addition, a correlation between PI3K pathway-related biomarkers and clinical responses will also be assessed as a secondary objective in this study.

7 Protocol and Data Development

7.1 Ethics

7.1.1 Institutional review board

This trial can be undertaken only after review and full approval of the protocol and a Patient Informed Consent Form has been obtained from a properly constituted IRB. This written approval must be dated and it must clearly identify the protocol, any amendments, the Patient Informed Consent Form, Investigator's Brochure, the name of the Principal Investigator (PI) and any applicable recruiting materials and subject compensation programs approved.

The decision concerning the conduct of the study will be made in writing to the SI. Copies of this decision and of all IRB correspondence will be kept on file at the study site; copies will be provided to the sponsor, Delta Clinical Research, LLC.

During the trial, the PI is required to send various documents to the IRB for review for:

1. Changes to the current protocol.
2. Changes to the Investigator's Brochure.
3. All protocol amendments and Patient Informed Consent Form revisions.
4. Reports of AEs/SAEs that are serious, unexpected, and associated with the investigational drug, and any life-threatening problems, or death.
5. Required progress reports.

If local IRB approval is acquired, the Delta Regulatory Affairs Office should be informed via research Standard Operation Procedures (SOP).

Particular attention is drawn to the FDA regulations regarding the IRB. The SI provides Delta with the necessary assurance that an IRB is responsible for the initial and continuing review and approval of the proposed clinical study in accordance with these regulations. At least once a year, the IRB will be asked to review and re-approve the clinical trial protocol; the request must be documented in writing. At the end of the trial, the SI will notify the IRB that the trial has been completed.

7.1.2 Patient informed consent

The informed consent should meet the requirements of the latest version of the Declaration of Helsinki and any applicable regulations and guidelines. It must be approved by an institutional ethics committee/IRB.

Prior to entry into the trial and before any protocol-required procedures are performed, the Treating Physician must explain the nature of the trial, its intended purpose, and the implications of participation to potential patients or to their legal representatives. They will be told about the possible risks and benefits, and the possible adverse experiences. They will be informed that patients' participation is voluntary, and that they may withdraw consent to participate at any time. They will also be informed that if patients choose not to participate in the trial, alternative treatments are available; such refusal will not prejudice further treatment of their disease. Potential patients or their legal representatives must be given the opportunity to ask questions about the trial protocol and the procedures involved.

Finally, each patient will be told that his or her records may be accessed by authorized personnel of Delta and other authorized individuals without violating the patient's confidentiality, to the extent permitted by the applicable laws and/or regulations. By signing the written Patient Informed Consent Form, the patient or his or her legal representative is authorizing such access. Following this explanation and prior to entry into the trial, the written, dated, and signed Patient Informed Consent Form must be obtained from each patient or his or her legal representative; a copy will be given to the person signing the form.

7.1.3 Confidentiality of records

The Treating Physician is required to retain, in a confidential manner, sufficient information on each patient (i.e., full name, current address, and social security number) so that the patient may be contacted by the FDA or by Delta should the need arise.

7.2 Study Records

7.2.1 Documentation

For each patient treated with the study drug(s), the Research Coordinator is required to prepare and maintain case histories that include all observations and other data pertinent to the investigation. This will include all source documents needed to verify the accuracy of all observations and other data contained in the eCRFs on each study patient.

The Treating Physician or his/her designee is required to retain the records related to the trial for a period of 2 years following the date a marketing application is approved for the indication being investigated. If no marketing application is to be filed or if the application is not approved for such indication, the records must be retained until 2 years after the investigation is discontinued and the regulatory agencies are notified.

The Treating Physician shall retain study drug disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by the site in which the study will be conducted, or for the period specified by Delta, whichever is longer. The Investigator must contact Delta prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Prior notice of such transfer will be given in writing to Delta.

7.2.2 Electronic case report form procedures

Data will be entered at the site using eCRFs. The Treating Physician or his/her designee is responsible for recording all data relating to the trial on the eCRFs. The Treating Physician must verify that all data entries on the eCRFs are accurate and correct. eCRFs must be completed **within 7 calendar days** of the end of each cycle and **within 7 calendar days** following completion of study therapy.

If an item is not available or is not applicable, it should be documented as such; **no blank spaces should be left on any eCRF.**

For patients removed from study, their eCRFs must then be completed **within 7 calendar days** of the date of removal from the study. Long-term survival information will be collected.

7.3 Monitoring/Site Visits

Study sites are subject to be monitored by the study sponsor or their designee, and/or by the Food and Drug Administration (FDA) or other regulatory agencies. To ensure accuracy, a minimal data set from the eCRFs will be compared with a subset of the original patient source documents during site visits. The monitor may also review case histories, laboratory certifications, IRB records, drug accountability records, and other source documentation. At all times, patients' confidentiality will be maintained.

Monitoring will take place at different sites. The monitoring plan will be developed by the study sponsor or their designee.

7.4 Modification of Protocol

Any changes to this protocol that affect study objectives, study design, study procedures, patient population, or significant administrative procedures will require a formal amendment to the protocol. Any proposed protocol amendments must be sent in writing to the applicable IRB. Prior to implementation, an amendment must be agreed upon by the SI and by Delta and approved by the applicable IRB.

General administrative changes to the protocol are minor corrections and/or clarifications that do not affect the manner in which the study is to be conducted. Such administrative changes will be agreed upon by the SI and will be documented in a memorandum. The applicable IRB will be notified of administrative changes according to applicable IRB guidelines.

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APPENDICES

Appendix 1 – Breast Cancer-Graded Prognostic Assessment (GPA)

Prognostic Factor	GPA Scoring Criteria					Patient Score
	0	0.5	1.0	1.5	2.0	
Karnofsky Performance Score	≤50	60	70-80	90-100	n/a	
Subtype	Basal	n/a	LumA	HER2	LumB	
Age, years	≥60	<60	n/a	n/a	n/a	
Sum total						

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Appendix 2 - Performance Status Criteria

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

Appendix 3 – CTCAE Grading

NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)
Version 4.0
Published: May 28, 2009 (v4.03: June 14, 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

DO NOT USE CTC VERSION 2.0 OR 3.0 TO GRADE TOXICITIES IN THIS STUDY!

Appendix 4 – Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) Eisenhauer EA, Therasse P, Bogaerts J, et al. Eur J Cancer. 2009 Jan;45(2):228-47.

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

Appendix 5 – Oral Medication Diary

US Oncology, Inc Study# 11-025

Drug Administration Record – to be completed by patient and returned at each visit

Please begin entries by checking the appropriate box that corresponds to the date treatment was started (Calendar Date). For example: If the patient starts treatment on January 24, 2014, check the box next to "24" under Calendar Date and continue entries from that date forward.

Patient Initials	
Arm	
Patient ID #	
Month	
Year	

Please return all copies of this form to the Clinical Research Coordinator at each clinic visit.

Calendar	Drug Taken	
Date	Yes	No
1		
2		
3		
4		
5		
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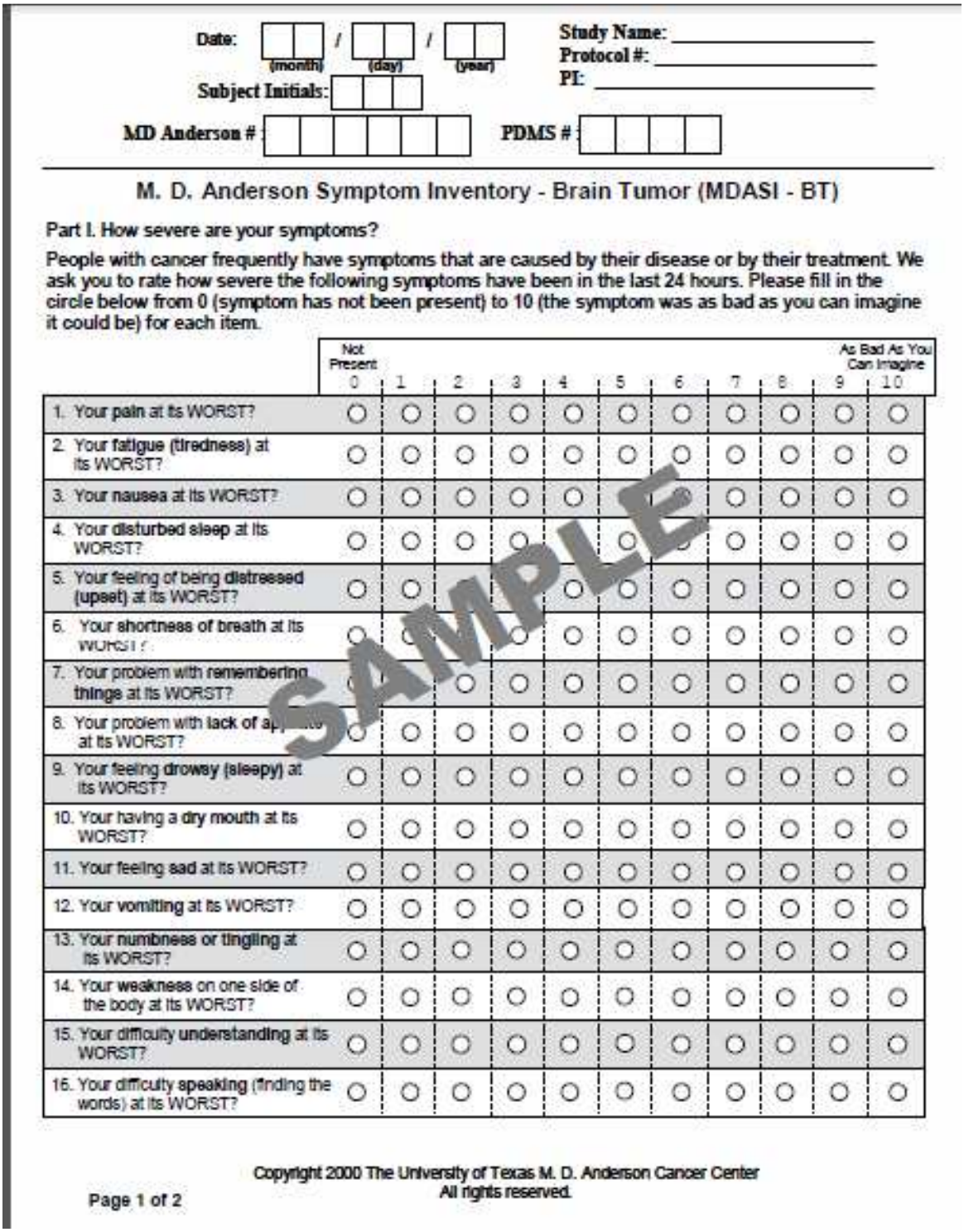
Appendix 6 – M.D. Anderson Symptom Inventory-Brain Tumor (MDASI – BT)

(The MD Anderson Symptom Inventory- Brain Tumor Module *Screening, every 8 weeks during treatment, End of Treatment (Window ± 3 business days). Any delay within this window is not a deviation.)



Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____

Protocol #: _____

PI: _____

Subject Initials: ☐☐☐

MD Anderson #: ☐☐☐☐☐☐

PDMS #: ☐☐☐☐

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue** (tiredness) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed** (upset) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of ap...** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy** (sleepy) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **difficulty understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **difficulty speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

SAMPLE

Page 1 of 2

Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: _____

MD Anderson #: ☐☐☐☐☐☐ PDMS #: ☐☐☐☐

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your seizures at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty concentrating at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your vision at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in appearance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in bowel pattern (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with [illegible]

Symptoms frequently interfere with how well we [illegible] function. How much have your symptoms interfered with the following items in the last 24 [illegible]:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity?	○	○	○	○	○	○	○	○	○	○	○
24. Mood?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?	○	○	○	○	○	○	○	○	○	○	○
28. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○