Ivy Foundation Early Phase Clinical Trials Consortium

A Phase 0/2 Study of Abemaciclib in Recurrent Glioblastoma

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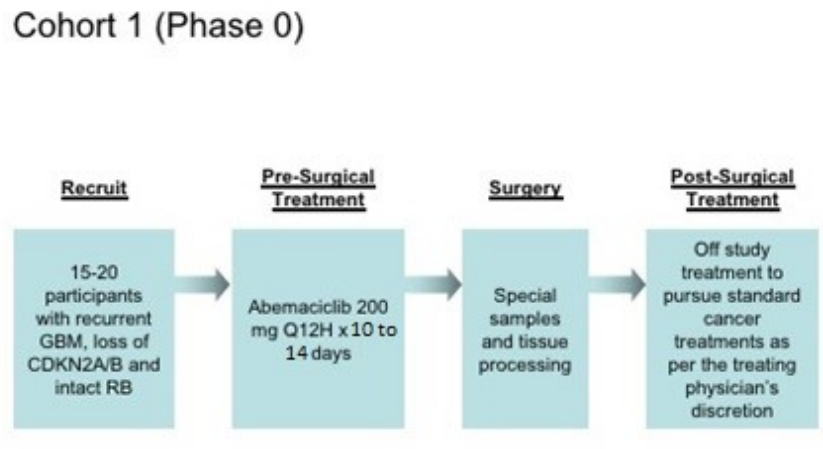
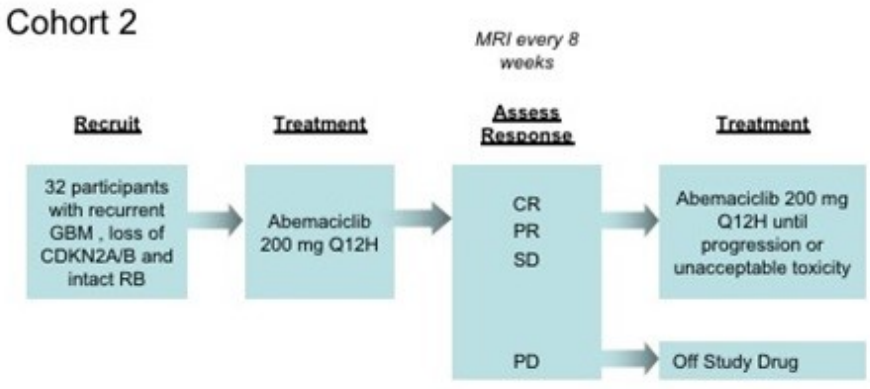
SCHEMA

Cohort 1 will be treated concurrently with Cohort 2





*The goal is to have 15 patients with adequate tissue for assessment of the primary objective. If sufficient tissue is not obtained from a patient, an additional patient will be added to the cohort. A maximum of 20 patients may be enrolled to this cohort.

1 cycle = 4 weeks

GBM= Glioblastoma
CDKN2A/B = Cyclin Dependent Kinase 4 and 6
RB = Retinoblastoma

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

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDK	Cyclin Dependent Kinase
CK	Creatine Kinase
CK-MB	Creatine Kinase - Muscle and Brain isoenzyme
CR	Complete Response
CRD	Clinical Research and Development
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
GBM	Glioblastoma
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HDL	High density lipoprotein
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection fraction
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
OS	Overall Survival
PD	Pharmacodynamic
PD	Progressive Disease
PFS	Progression Free Survival
PFS6	6 Month Progression Free Survival

PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time (also known as APTT)
QTc	QT interval (corrected)
RANO	Response Assessment in Neuro-Oncology
RB	Retinoblastoma
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
WBC	White Blood Count
WCBP	Women of Childbearing Potential
WHO	World Health Organization

1. OBJECTIVES

1.1 Study Design

This will be an open label, multi-center, phase 0/II trial of abemaciclib (LY2835219) in participants with recurrent glioblastoma (GBM) at their first or second relapse. Patients must have documented evidence of CDKN2A/B loss and intact RB in previously obtained tumor tissue by exome sequencing, copy number analysis [e.g. array comparative genomic hybridization (CGH)] and/or IHC for RB prior to enrollment into the study.

In the phase 0 surgical arm (cohort 1), fifteen participants who require reoperation and have evidence of CDKN2A/B loss and intact RB from a prior tumor sample will receive a short preoperative course of abemaciclib for 10-14 days. Tissue will be used to investigate the ability of abemaciclib to pass through the blood brain barrier (BBB), achieve therapeutic concentrations in the tumor, and inhibit cellular proliferation in tumor tissue. Immunohistochemistry analysis for pRB, KI67, p21, and cleaved caspase 3 in tumor tissue obtained during the surgery as compared with tissue from a prior surgery will be used as a measure of decreased tumor cell proliferation and increased tumor cell death. In addition, as exploratory aims, we will perform functional biomarker analysis on live cells and patient derived cell lines and xenografts obtained from cohort 1 patients in order to determine their response to abemaciclib and investigate the associations between clinical outcomes and immunologic effects of abemaciclib. After surgery, cohort 1 participants will come off study treatment and pursue standard cancer treatments as per the treating physician's discretion.

The phase II treatment arm (cohort 2) will be comprised of 32 participants not requiring surgery. Participants will receive treatment with abemaciclib for each 28 day cycle (if participant tolerates first cycle of treatment well, abemaciclib may be increased for all subsequent cycles if the investigator determines that it is in the best interest of the patient). The primary endpoint is to determine the overall efficacy of abemaciclib as determined by six-month progression free survival (PFS6). Participants will remain on treatment until tumor progression, as long as there are no unacceptable toxicities. Responses will be assessed by clinical examinations every 4 weeks and MRI scans every 8 weeks. Responses determined using the new Response Assessment in Neuro-Oncology (RANO) criteria (Wen et al., 2010).

Limited pharmacokinetic studies will be performed to ensure that there is no significant difference in patients with GBM compared to other solid tumors. Because the extent to which abemaciclib is metabolized by cytochrome P450 enzymes such as 3A4, is unknown, the concurrent use of enzyme-inducing anti-epileptic drugs (EIAEDs) such as phenobarbital, phenytoin, carbamazepine, and oxcarbazepine will not be permitted as these drugs may result in reduced exposure to abemaciclib. Since the vast majority of glioblastoma patients are no longer taking EIAEDs, this will not significantly affect patient accrual.

1.2 Primary Objectives

1.2.1 Cohort 1

- To evaluate abemaciclib concentration in tumor tissue.

1.2.2 Cohort 2

- To investigate the treatment efficacy of abemaciclib in participants with recurrent GBM as measured by 6-month progressive-free survival (PFS6).

1.3 Secondary Objectives

1.3.1 Cohort 1

- To evaluate effects of abemaciclib on phospho-RB (S807/811), tumor cell proliferation (Ki67) and tumor cell death (CC3, p21) by immunohistochemistry (IHC).
- To investigate pharmacokinetics of abemaciclib in participants with recurrent GBM.
- To investigate the safety profile of abemaciclib in participants with recurrent GBM.

1.3.2 Cohort 2

- To investigate the radiographic response (RR) to abemaciclib.
- To investigate median progression free survival (PFS) and overall survival (OS) of participants with recurrent GBM receiving treatment with abemaciclib.
- To investigate pharmacokinetics of abemaciclib in participants with recurrent GBM.
- To investigate the safety profile of abemaciclib in participants with recurrent GBM.

1.4 Exploratory Objectives

1.4.1 Cohort 1

- To investigate associations between clinical outcomes and immunologic effects of abemaciclib including quantitative assessments of tumor infiltrating lymphocytes (TIL) that express PD-1, delineation of PD-L1+ cells in the tumor microenvironment, assessment of immune pathways pretreatment and posttreatment, and quantitative assessment of T cell receptors from tumor samples pretreatment and posttreatment.
- To investigate the effects of abemaciclib on cellular programs as characterized using single-cell RNA-sequencing based on tumor samples posttreatment in comparison to historical untreated controls.
- To investigate the effects of abemaciclib on tumoral antigen presentation and the immune milieu of the tumor microenvironment based on tumor samples posttreatment in comparison to historical untreated controls.
- To investigate the effects of abemaciclib on patient-derived cells (PDC), cell lines (PDCL) and xenografts (PDX) established from patients on the study.

1.4.2 Cohort 2

- To correlate response to treatment with molecular phenotype of pre-treatment tumor (Oncopanel sequencing and array CGH copy number analysis);
- To investigate the mechanisms of resistance to abemaciclib by examining tumor tissue obtained from patients who progress on treatment, when available, with pretreatment tumor.

2. BACKGROUND

2.1 Glioblastoma

Glioblastomas are the most common type of malignant primary brain tumors in adults and accounts for 15.4% of all primary brain tumors (Ostrom et al., 2014). The annual incidence rate of GBM in the United States is 3.19 per 100,000. Despite optimal treatment with surgery, radiation therapy, and chemotherapy, the prognosis remains poor. In 2005, results from a randomized phase III trial indicated that the addition of temozolomide chemotherapy to radiation therapy for treatment of newly-diagnosed GBM prolonged median overall survival (OS) from 12.1 to 14.6 months (Stupp et al., 2005). For patients with glioblastomas whose tumors recur, the median time to tumor progression is only 9 weeks and median survival is 25 weeks (Wong et al., 1999). Once patients develop tumor progression, conventional chemotherapy is generally ineffective. Several reasons account for this poor response to chemotherapy including reduced drug delivery as a result of the blood-brain barrier, intrinsic resistance to many cytotoxic agents, tumor hypoxia, and a relatively low growth fraction. There is a need for more effective therapies based on novel mechanisms of action (Wen & Kesari, 2008).

Role of the CDK4/6 –RB Pathway in the Molecular Pathogenesis of Glioblastomas

Deregulation of the cyclin-dependent kinases (CDK) 4 and 6 (cdk4/6)–cyclin D-INK4—retinoblastoma protein (Rb) signaling pathway is among the most common aberrations found in glioblastomas with more than 80% of patients estimated to be affected (Brennan et al., 2013). This pathway is most commonly altered by homozygous deletion of CDKN2A/B, and less commonly by deletion/mutation of CDKN2C and RB1, or genomic amplification of CDK4, CDK6, and individual D-type cyclins (Brennan et al., 2013; Dunn et al., 2012; Wiedemeyer et al., 2008). Recent molecular profiling of GBM has further highlighted the critical role of CDK4/6 activation in the pathogenesis of this devastating tumor (Brennan et al., 2013). In preclinical studies with the CDK4/6 inhibitor palbociclib (PD-0332991) in GBM cell lines and orthotopic models, there was potent induction of G1 cell cycle arrest, and induction of senescence in each of 16 retinoblastoma protein (Rb)–proficient cell lines regardless of other genetic lesions, whereas 5 cell lines with homozygous inactivation of Rb were completely resistant to treatment, suggesting that Rb status is the primary determinant of potential benefit from this therapy (Michaud et al., 2010). The combination of palbociclib and radiation therapy resulted in significantly increased survival benefit compared with either therapy alone (Michaud et al., 2010). Another study produced somewhat similar findings with GBM lacking CDKN2A/B expression and with non-amplified CDK4 and wild-type RB status showing more susceptibility

to Cdk4/6 inhibition using palbociclib (PD0332991) (Cen et al., 2012).

2.2 Abemaciclib (LY2835219)

Abemaciclib (LY2835219) is a selective and potent small molecule CDK4/6 dual inhibitor that is hypothesized to arrest tumor growth through prevention of cell cycle progression through the G1 restriction point. In humans, one study has been completed (I3Y-MC-JPBD [JPBD]) and 13 studies are ongoing including I3Y-MC-JPBA, I3Y-MC-JPBB, I3Y-JE- JPBC, I3Y-MC-JPBE, I3Y-MC-JPBH, I3Y-MC-JPBJ, and I3Y-MC-JPBN.

Absorption, Distribution, Metabolism, and Excretion

Abemaciclib (LY2835219) demonstrates moderate to high bioavailability in preclinical species. In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 17 to 38 hours across the dose range tested. At a single dose of 200 mg, the mean apparent oral clearance is 38.3 L/h with high inter-individual variability (105% coefficient of variation [CV]) and the apparent volume of distribution is large at 1300 L (96% CV). Following oral administration, abemaciclib was extensively metabolized followed by biliary excretion of metabolites.

Based on Study JPBD and in vitro data, CYP3A is responsible for abemaciclib metabolism, the primary route of clearance. Strong CYP3A inhibitors may increase abemaciclib exposures, and strong inducers may decrease abemaciclib exposures. Abemaciclib and its major metabolites did not substantially inhibit CYP enzymes in human liver microsomes; however, there was downregulation of mRNA for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A. Caution should be exercised when coadministering abemaciclib with narrow therapeutic drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A.

The abemaciclib (LY2835219) radioactivity associated with [14C] abemaciclib (LY2835219) distributes well into tissues and organs, with radioactivity concentrations measurable through 24 hours post-dose in various parts of brain in rat. Abemaciclib (LY2835219) therefore distributes extensively to the brain in vivo and produces a statistically significant and dose dependent improvement in survival in a rat orthotopic brain tumor model. Median survival was improved 8 and 12 days compared to vehicle following daily oral treatment at 40 mg/kg and 80 mg/kg for 21 days, respectively. Preclinical data demonstrates that abemaciclib (LY2835219 mesylate inhibits CDK4/6 to induce G1 arrest specifically in Rb-proficient tumors. In primary human tumor xenograft models, abemaciclib (LY2835219) also demonstrates tumor growth delay and a prolongation of survival. Abemaciclib (LY2835219) was initiated day 6 post tumor cell injection as oral gavage once daily at either 45 or 90 mg/kg/administration. Normalized bioluminescence was reduced in tumors treated with either dose level, which led to a statistically significant improvement in survival. In GBM human xenograft models, growth inhibition was generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 days.

In another study orally dosed abemaciclib significantly increased survival in a rat orthotopic U87MG xenograft model compared with vehicle-treated animals, and efficacy coincided with a dose-dependent increase in unbound plasma and brain exposures in excess of the CDK4 and CDK6 Ki values. Abemaciclib increased survival time of intracranial U87MG tumor-bearing rats

similar to temozolomide (TMZ), and the combination of abemaciclib and TMZ was additive or greater than additive. These data show that abemaciclib crosses the blood–brain barrier and confirm that both abemaciclib and another CDK4 and CDK6 inhibitor, palbociclib, reached unbound brain levels in rodents that are expected to produce enzyme inhibition; however, abemaciclib brain levels were reached more efficiently at presumably lower doses than palbociclib and were potentially on target for a longer period of time.(Raub et al., 2015).

In other preclinical data we studied effects of abemaciclib (LY2835219) on a panel of GBM patient derived cell line models (PDCLs) which faithfully recapitulate the biology and genotype of GBM patients along with their diversity. This work shows that the initial biomarker hypothesis that CDKN2A homozygous deletion (or greater than 1 copy loss) is associated with increased sensitivity to the drug and CDK4 amplification is associated with relative resistance.

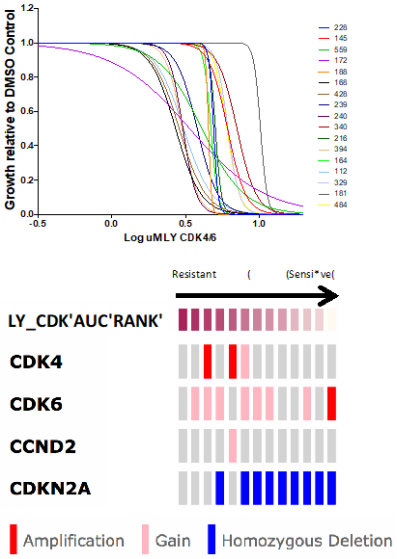

Figure 1. GBM PDCLs treated with LY2835219 (Abemaciclib) show differential response based on genotype with CDKN2A deleted lines (>1 copy loss) being more sensitive than lines with intact CDKN2A.. (Ligon and Wen, unpublished)

Cerebrospinal fluid (CSF) samples were collected from a limited number of patients with brain metastases in Study JPBA on Day 15 of Cycle 1 after repeated Q12H dosing. In general, abemaciclib concentrations in CSF were consistent with unbound plasma concentrations. The metabolite concentrations were lower than abemaciclib concentrations and in some patients below the lower limit of quantitation (1 ng/mL).

Dosing and Method of Administration

Abemaciclib has been administered orally on Days 1 through 28 of a 28-day cycle. In Study JPBA, the MTD for humans when administered as a single agent is 200 mg Q12H. During the tumor-specific expansion phases of JPBA, patients initially received abemaciclib at the MTD of 200 mg Q12 hours. A preliminary interim safety review with data from 56 patients indicated that 29 patients experienced diarrhea possibly related to study drug: 17 Grade 1 (30%), 9 Grade 2 (16%), 3 Grade 3 (5%), none Grade 4 (0%), and none Grade 5 (0%). Based on the frequency of Grade 1/2 diarrhea and the observation of clinical activity at doses below the MTD, the initial starting dose was changed to 150 mg every 12 hours to gain additional PK data and clinical experience around safety/tolerability. Based on this further clinical experience (demonstrating that the diarrhea experienced by patients is manageable with standard anti-diarrheal agents such as loperamide) the study was further amended to again allow starting doses of 200 mg Q12H. Therefore, for safety, the starting dose of abemaciclib in this phase 2 study in recurrent GBM will be 150 mg Q12H. Abemaciclib may be escalated at the start of Cycle 2 to 200 mg Q12H if the investigator determines that it is in the best interest of the patient.

Dosages for pediatric and geriatric populations are not known at this time. There is no information for dosage adjustments in patients with renal insufficiency, hepatic insufficiency, or

concomitant disease, or who are undergoing dialysis.

Safety and Efficacy

Validated safety data for 352 patients treated with abemaciclib in Studies JPBA, JPBB, JPBC, JPBH, JPBJ, and JPBN are available. Cumulatively, the most common TEAEs (≥10%) possibly related to study drug for patients receiving abemaciclib either as a single agent, with endocrine therapy, or with chemotherapy, are diarrhea (64.2%), nausea (44.3%), fatigue (39.8%), neutropenia (27.0%), vomiting (24.1%), thrombocytopenia (21.3%), leukopenia (21.0%), anemia (17.6%), decreased appetite (17.6%), and blood creatinine increased (14.5%).

The majority of deaths reported for patients in the studies with available safety data were due to study disease.

As of 14 October 2014, 31 patients in Studies JPBA, JPBB, JPBC, JPBE, JPBH, JPBJ, and JPBN experienced 43 SAEs that were reported as possibly related to study drug. SAEs that were possibly related to study drug and experienced by more than 1 patient included diarrhea (5 patients), dehydration (4 patients), neutropenia and pneumonia (3 patients each), and anemia, confusional state, nausea, pyrexia, and sepsis (2 patients each).

Study JPBA was a phase 1 study of abemaciclib in patients with advanced cancer and included some patients with primary brain tumors or brain metastases. Plasma and CSF concentrations of abemaciclib were obtained in patients with primary brain tumors or brain metastases after reaching steady state with < 2.5 hours between plasma and CSF sampling. The results supported the preclinical observations of distribution extensively in the CSF. Seventeen patients with GBM that had progressed or recurred after radiotherapy and/or chemotherapy enrolled in the tumor-specific expansion phase (Part C) of study JPBA. Abemaciclib was given as a single agent at a dose of 200 mg orally every 12 hours on Days 1 through 28 of a 28-day cycle. In this progressive/recurrent GBM cohort of unselected patients, the disease control rate (DCR = response + stable disease) was 17.6% and median PFS was 1.1 months. It should be noted that 13 of the 17 patients were heavily pretreated patients who had failed bevacizumab. In the 4 heavily pretreated patients who had not received bevacizumab, 2 patients experienced prolonged disease stability (1 patient had received 19 cycles and 1 patient had received 24 cycles at data cutoff). Both remained on treatment with stable disease at data cutoff.

Clinical Pharmacodynamics

In the colorectal (Colo-205) xenograft model and skin biopsies from patients in Study I3Y-MC-JPBA (JPBA), abemaciclib inhibited phosphorylated Rb [pRb], and topoisomerase II alpha [TopoIIα] at clinically relevant doses and exposures.

2.3 Rationale For Phase II Trial of Abemaciclib in Recurrent Glioblastomas

Deregulation of the cdk4/6–cyclin D-INK4—Rb signaling pathway is among the most common genomic aberrations found in GBM (78% of patients) and plays an important role in its pathogenesis (TCGA 2008; Brennan, Verhaak et al. 2013). *In vitro* and *in vivo* studies with

cdk4/6 inhibitors demonstrate potent induction of G1 cell cycle arrest and antitumor activity (Cen et al., 2012; Michaud et al., 2010; Raub et al., 2015). Studies also suggest that Rb status is the primary determinant of potential benefit from this therapy (Michaud, Solomon et al. 2010). Abemaciclib (LY2835219) is a selective and potent small molecule CDK4/6 dual inhibitor that distributes extensively in brain. In human GBM xenograft models, abemaciclib demonstrated tumor growth delay. For these reasons, we propose a phase II study of abemaciclib in participants with recurrent glioblastoma with loss of CDKN2A/B and intact RB to evaluate its antitumor activity (Cohort 2).

2.4 Rationale For Phase 0 Study of Abemaciclib in Recurrent Glioblastomas

We will examine a PK/PD cohort of 15 participants (Cohort 1) where abemaciclib will be administered for 10-14 days prior to surgery and treated tumor specimens will be examined for drug concentrations and evidence of inhibition of cellular proliferation (KI67) cell death (CC3 and p21) and decreased phospho-Rb (pRb) in tumor tissue to confirm the ability of abemaciclib to pass through the blood-brain barrier and produce a pharmacodynamic effect *in vivo*.

Data from Jean Zhao and colleagues also suggest that CDK4/6 inhibitors increase tumor immunogenicity (Goel et al., 2017). Based on murine models of solid tumors including GBM, selective CDK4/6 inhibitors not only induce tumor cell cycle arrest, but also promote anti-tumor immunity via two distinct elements: first, CDK4/6 inhibitors activate tumor cell expression of endogenous retroviral elements, thus increasing intracellular double-stranded RNA levels. This in turn stimulates production of type III interferons and thence increases tumor antigen presentation; second, CDK4/6 inhibitors markedly suppress the proliferation of regulatory T cells (Tregs). Mechanistically, each of these phenomena is associated with reduced activity of DNA methyltransferase 1 (in tumor cells and Tregs respectively), the expression of which is controlled by the CDK4/6-RB-E2F pathway. Ultimately, this leads to cytotoxic T cell-mediated clearance of tumor cells, which is further enhanced by the addition of immune checkpoint blockade. In the same PK/PD cohort of 15 participants (Cohort 1) where abemaciclib will be administered prior to surgery, treated tumor specimens will be examined for immunologic biomarkers such as the density of T lymphocytes within tumor tissue and the T cell receptor (TCR) clonality.

As the study continued, the nonsurgical cohort (Cohort 2) completed accrual while the surgical cohort (Cohort 1) remained open. Outcomes data were reviewed in the nonsurgical cohort (Cohort 2) demonstrating limited benefit from abemaciclib monotherapy with a PFS6 rate of 9.37% [95% CI, 2.4%, 22.27%], median PFS 55 days [95% CI, 49, 56], and median OS 384 days [95% CI, 228, 488]. Nonetheless, a surgical cohort still provides valuable information to understanding why abemaciclib has limited activity in recurrent GBM patients and whether it helps enhance the antitumor immune response (Goel et al., 2017). Therefore, the study was amended further to convert the remaining slots in the surgical cohort (Cohort 1) into a Phase 0 study. The study design remains the same (pretreatment with abemaciclib followed by surgery with correlative studies) except that participants will come off study treatment after surgery and pursue standard cancer treatments as per the treating physician's discretion. The purpose of this phase 0 study is not to treat the tumor but to determine tumor tissue PK and PD. This phase 0 study does not replace routine cancer treatment.

2.5 Correlative Studies Background

Cohort 1: In this cohort, patients with recurrent GBM will receive drug for 10-14 days prior to a reoperation. Tumor will be resected and analyzed for:

1) Pre-treatment tumor will be genotyped with next generation sequencing and the results correlated with outcome if not previously performed.
2) Drug concentration using liquid chromatography - tandem mass spectrometry (LC-MS/MS). Tumor concentration will be compared to plasma drug concentrations to determine if therapeutic levels of abemaciclib can be achieved in both enhancing and non-enhancing tumor.
3) Tumor tissue will be analyzed by IHC and proteomics analysis for Phospho-Rb, (S807/811) proliferation (Ki-67), and apoptosis (cleaved caspase 3) to determine if abemaciclib can achieve a pharmacodynamic effect in enhancing and non-enhancing tumor tissue. These data will be compared to results from the patient's prior archived tumor tissue not exposed to abemaciclib obtained from each participant's prior surgery, and to results from unrelated glioblastoma patients (n=10) with tumor tissue from pre- and post-treatment with standard of care RT+TMZ.
4) Tumor tissue will be analyzed for quantitative assessment of TIL that express PD-1, delineation of PD-L1+ cells in the tumor microenvironment (macrophage vs. tumor cells), immune response based multiplex gene expression analysis in tumor samples pre- and post-treatment, and quantitative assessment of T cell receptors in tumor samples pre- and post-treatment
5) Tumor tissue will be analyzed for tumoral expression of major histocompatibility complex type I and II, markers of T-cell exhaustion, type III interferon production and profiling of the immune milieu of the tumor microenvironment by multiplexed immunofluorescence (IF), and activation of abemaciclib-induced intrinsic anti-tumor immunity by gene expression analysis.
6) If sufficient tumor is available, fresh patient derived cells (PDC), patient-derived cell lines (PDCL), and patient derived xenografts (PDX) will be attempted to be generated.
7) Fresh cells or PDCL/PDX models will undergo functional sensitivity testing to abemaciclib or studied using genomics or expression analysis.

Cohort 2: Tumor from the participant's surgery prior to enrolling onto the study will be studied for correlative markers.

1) Pre-treatment tumor will be genotyped with next generation sequencing and the results correlated with outcome if not previously performed.
2) IHC analysis of pRB, Ki67, and CC3 will be performed for correlation with outcome.
3) Analysis of any cell lines derived from prior surgery will be studied if available.

3. PARTICIPANT SELECTION

Screening evaluations are detailed in Study Calendar (Section 10). All assessments are to occur within 14 days of registration except where otherwise noted. The participant must be thoroughly informed of 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 participant prior to enrollment.

Following registration, any additional laboratory assessments obtained prior to start of treatment will not be used to re-confirm eligibility. Please refer to Section 6.2 and Table 6.3 Dosing Delays/Dose Modifications for toxicity management between registration and start of study treatment.

3.1 Eligibility Criteria

All participants must meet the following criteria on screening examination to be eligible to participate in the study:

1. Participants must be able to understand and willing to sign a written informed consent document.
2. Participants must be able to adhere to the dosing and visit schedules and agree to record medication times accurately and consistently in a daily diary.
3. Participants must be at least 18 years old on day of signing informed consent.
4. Participants must have a Karnofsky Performance Status (KPS) ≥ 60 (see Appendix A).
5. Participants must be able to swallow tablets.
6. Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy of the trial are eligible.

   NOTE: consultation with the Overall PI is highly recommended if enrollment of a participant with a prior or concurrent malignancy is being pursued.

Nature of illness and treatment history

7. Participants must undergo central pathology review to histologically confirm the diagnosis of glioblastoma, IDH-wildtype; glioblastoma variants; or astrocytoma, IDH-mutant, WHO grade 4 (1 unstained slide or 1 H&E slide must be submitted to and reviewed by a pathologist at the DFCI Coordinating Center prior to enrollment of the participant for central pathology review).
8. To be eligible for the study all participants (Cohort 1 and 2) are required to provide genomic profiling data from assays performed in a CLIA-certified lab. A sequencing-based assay is required and must include reporting of the RB1 gene in explicit terms within the report. Only sequencing assays that include coverage of *all* exons of the RB1 gene are able to be utilized (most commonly called a targeted exome assay; e.g. Oncopanel, Impact, FoundationOne). In addition, patients must provide a report of copy

assessment which reports status of RB1. The reporting may be from a copy array (ideally Oncoscan SNP array or Agilent array CGH) or can also be from sequencing assay if copy status is explicitly provided with quantitative information regarding the status of relevant genes. Specifically, the reporting should provide the following information with respect to relevant biomarkers required for enrollment to the study as listed below.

Results from genomic profiling must be sent to the DFCI Coordinating Center prior to enrollment of the participant for central pathology review. Central pathology can provide feedback on reports if requested to help in assessing status as needed.

- Inactivation of CDKN2A/B or C in the tumor by homozygous deletion (evidence for more than single copy loss for any of the genes defined as array CGH/SNP log2 ratio of <0.3 by array CGH; or from sequencing data with sufficient coverage for evaluation). Rearrangement/evidence or intragenic breaks by copy or sequencing assay also will be considered eligible for study (any copy status).

OR

- CDK4 or CDK6 high-level amplification. (The amplicon size must be <10Mb and the magnitude the gain must be log2 ratio >1.5 or estimated as >10 copies).

AND

- Validation of wild-type RB status (no deletion/losses more than single copy by copy number or sequencing data; and/or no inactivating mutations or rearrangements by sequencing).

9. Participants must be at first or second relapse of GBM. Relapse is defined as progression following therapy. The intent is that patients had no more than 2 prior therapies.
10. Participants must have shown unequivocal evidence for tumor progression by MRI or CT scan.
    - For Cohort 2 subjects, CT or MRI within 14 days prior to study registration. For Cohort 2, corticosteroid dose must be stable or decreasing for at least 5 days prior to the scan. If steroids are added or the steroid dose is increased between the date of the screening MRI or CT scan and the start of treatment, a new baseline MRI or CT is required.
    - For Cohort 1 subjects, CT or MRI should be performed ideally within 14 days prior to study registration, but because the screening MRI for this subset of subjects will not be used for evaluation of response, it is acceptable for this MRI/CT to have been performed greater than 14 days prior to registration if unavoidable. Furthermore, for this same reason, fluctuation in corticosteroid dose around this MRI does not warrant repeat scan so long as there is documented unequivocal evidence of tumor progression available.
    - For Cohort 1 subjects, there must be > $2cm^2$ enhancing tissue available for resection and submission for study correlatives as determined by local treating team.
11. Confirmation of availability of sufficient tissue from a prior surgery for correlative

studies is required prior to enrollment; these samples must be sent to the DFCI Coordinating Center within 60 days of registration. Cohort 1 participants must have sufficient FFPE tissue from any surgery. Cohort 2 participants must have tissue from biopsy or resection from the most recent recurrence surgery.

The following amount of archived tissue is required:

- 20 unstained formalin fixed paraffin embedded (FFPE) sections (standard 5 micrometer thickness)

NOTE: if the above-mentioned tissue is not available from the most recent surgery revealing GBM, participants may be enrolled with tissue available from any prior surgery revealing GBM with prospective approval from the Overall PI.

12. An interval of at least 12 weeks from the completion of radiation therapy to start of study drug unless there is a new area of enhancement consistent with recurrent tumor outside the radiation field (defined as the region outside the high-dose region or 80% isodose line) or there is unequivocal histologic confirmation of tumor progression. If recurrence is outside the radiation field or there is histologic confirmation of tumor progression, then an interval of at least 14 days must have elapsed from completion of radiation therapy to start of study drug and participants must have fully recovered from the acute effects of radiotherapy.
13. Participants must have recovered to grade 0 or 1 or pre-treatment baseline from clinically significant toxic effects of prior therapy (including but not limited to exceptions of alopecia, laboratory values listed per inclusion criteria, and lymphopenia which is common after therapy with temozolomide).
14. From the projected start of scheduled study treatment, the following time periods must have elapsed:
    - 4 weeks or 5 half-lives (whichever is shorter) from any investigational agent;
    - 4 weeks from cytotoxic therapy (except 23 days for temozolomide; 6 weeks from nitrosoureas);
    - 4 weeks from antibodies;
    - 4 weeks or 5 half-lives (whichever is shorter) from other anti-tumor therapies.
    - 2 days from Novo-TTF
15. Participants with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of progressive disease based upon nuclear imaging, MR spectroscopy, perfusion imaging or histopathology.
16. Participants having undergone recent resection or open biopsy or stereotactic biopsy of recurrent or progressive tumor will be eligible for Cohort 2 as long as the following conditions apply:
    - They have recovered from the effects of surgery.
    - Residual disease following resection of recurrent tumor is not mandated for eligibility. To best assess the extent of residual disease post-operatively, an MRI

or CT scan should ideally have been performed no later than 96 hours following surgery, or at least 28 days post-operatively, but scans performed outside of this window are considered acceptable if no alternative is available. In either case, the baseline/screening MRI must be performed within 14 days prior to registration. If the participant is taking corticosteroids, the dose must be stable or decreasing for at least 5 days prior to the scan. If steroids are added or the steroid dose is increased between the date of the screening MRI or CT scan and the start of treatment, a new baseline MRI or CT is required.

Clinical labs – performed within 14 days prior to registration

17. Hematology:
    - Absolute neutrophil count (ANC) ≥ 1.5 x K/μL
    - Platelet count ≥ 100 x K/μL
    - Hemoglobin ≥ 8.0 g/dL
18. Biochemistry:
    - Total serum calcium (corrected for serum albumin as needed) or ionized calcium within institution's normal range.
    - Magnesium within institution's normal range.
    - AST (SGOT) and ALT (SGPT) ≤ 3.0 x institution's ULN
    - Serum bilirubin ≤ 1.5 x institution's ULN. Patients with Gilbert's syndrome with a total bilirubin ≤ 2.0 times ULN and direct bilirubin within normal limits are permitted.
    - Serum creatinine ≤ 1.5 x institution's ULN or calculated 24-hour creatinine clearance ≥ 50 mL/min
    - Serum amylase ≤ 1.5 x institution's ULN
    - Serum lipase ≤ 1.5 x institution's ULN
19. Coagulation studies:
    - INR < 2.0
    - PTT ≤ institution's ULN, unless receiving therapeutic low molecular weight heparin or oral factor Xa inhibitors.

Pregnancy and Reproduction

20. Based on findings in animals, abemaciclib can cause fetal harm when administered to a pregnant woman. For this reason, women of child-bearing potential (WOCBP) must agree to use a highly effective contraceptive method **during the treatment period and for 3 weeks following the last dose of abemaciclib**. Men must agree to use a reliable method of birth control and to not donate sperm during the study and for at least 3 weeks following the last dose of abemaciclib. Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.

- 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 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.

21. Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to first dose of abemaciclib.

3.2 Exclusion Criteria

Participants who meet any of the following criteria will not be eligible for admission into the study.

Pathology

1. Prior evidence of 1p/19q co-deletion.

Previous therapies

2. Participants who have received prior treatment with a CDK4/6 inhibitor.
3. Participants who have received anti-VEGF targeted agents (e.g. bevacizumab, cediranib, aflibercept, vandetanib, XL184, sunitinib etc).

Concomitant medications

4. Participants taking an enzyme-inducing anti-epileptic drug (EIAED): phenobarbital, phenytoin, fosphenytoin, primidone, carbamazepine, oxcarbazepine, eslicarbazepine, rufinamide, and felbamate. Participants must be off any EIAEDs for at least 14 days prior to starting study drug. A list of EIAEDs and other inducers of CYP3A4 can be found in Appendix D.
5. Participants taking a drug known to be a strong inhibitor or inducer of isoenzyme CYP3A (Appendix D). Participant must be off CYP3A inhibitors and inducers for at least 14 days prior to starting study drug. *NOTE: participants must avoid consumption of Seville oranges (and juice), grapefruits or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A4 interaction.*
6. Participants receiving any other investigational agents.
7. Current use of herbal preparations/medications, including but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Participants should stop using these herbal medications 7 days prior to first dose of study drug.
8. Current use of warfarin sodium or any other coumadin-derivative anticoagulant. Participants must be off Coumadin-derivative anticoagulants for at least 7 days prior to starting study drug. Low molecular weight heparin is allowed.

9. Requires treatment with high dose systemic corticosteroids defined as dexamethasone > 4 mg/day or bioequivalent for at least 3 consecutive days within 2 weeks of registration.

Other illnesses

10. History of allergic reactions attributed to compounds of similar chemical or biologic composition to abemaciclib.
11. History of intratumoral or peritumoral hemorrhage if deemed significant by the treating investigator. If there are questions, the treating investigator should contact the study Overall P.I., Eudocia Quant Lee, MD, at 617-632-2166 or eqlee@partners.org.
12. Serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study including, but not limited to interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment (e.g. estimated creatinine clearance <30ml/min), history of major surgical resection involving the stomach or small bowel, preexisting Crohn's disease or ulcerative colitis, chronic liver disease (e.g., cirrhosis, hepatitis), pancreatitis, chronic pulmonary disease, or psychiatric illness/social situations that would limit compliance with study requirements. Subjects must be free of any clinically relevant disease (other than glioma) that would, in the treating investigator's opinion, interfere with the conduct of the study or study evaluations.
13. Participant has an active systemic bacterial (requiring intravenous antibiotics at time of initiating study treatment), fungal infection, and/or detectable viral infection (for example, human immunodeficiency virus positivity, known active hepatitis B [for example, hepatitis surface antigen positive], or known active hepatitis C). Screening is not required for enrollment.
14. Participants with diarrhea ≥ CTCAE grade 2
15. Participant has active cardiac disease including any of the following:
    a. Angina pectoris that requires the use of anti-anginal medications
    b. Supraventricular and nodal arrythmias requiring a pacemaker or not controlled with medication
    c. Conduction abnormality requiring a pacemaker
    d. Valvular disease with document compromise in cardiac function
    e. Symptomatic pericarditis
16. Participant has a history of cardiac dysfunction including any of the following:
    - Myocardial infarction within the last 6 months prior to start of study drug, documents 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)
    - Active cardiomyopathy

- Congenital long QT syndrome
- History of syncope of cardiovascular etiology
- History of sudden cardiac arrest
- History of ventricular arrhythmias of pathological origin including, but limited to, ventricular tachycardia and ventricular fibrillation

17. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of abemaciclib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive small bowel resection). Participants with unresolved diarrhea ≥ CTCAE grade 2 will be excluded as previously indicated.
18. Participants who have undergone major systemic surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
19. Participants who are pregnant or breastfeeding.
20. Participants with history of known coagulopathy that increases risk of bleeding or a history of clinically significant hemorrhage within 12 months of start of study drug.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

All sites should email the Study Coordinator at NeuroOnc_Coor@dfci.harvard.edu to verify slot availability.

4.1 General Guidelines for DF/HCC Institutions

DF/HCC institutions will register eligible participants with the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

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

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the DFCI Coordinating Center by a Coordinating Center team member. All sites should email the Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu to verify slot availability.

The required forms can be found in Appendix B, Section 3.7.1. Following registration, participants should begin protocol therapy as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Coordinating Center should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, please refer to Appendix B, Section 3.7.1.

To complete the registration process, the Coordinator will follow DF/HCC policy (SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level to the participating site.

5. TREATMENT PLAN

Cohort 1 will be conducted concurrently with Cohort 2.

5.1 Treatment Regimen

All participants will initiate treatment with abemaciclib as soon as feasible following registration. The study drug abemaciclib will be administered on an outpatient basis (except on day of surgery for Cohort 1 participants). The investigator will instruct the participant to take the study drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Abemaciclib will be administered on a continuous twice daily dosing schedule. Participants should be instructed to take the dose of 150 mg abemaciclib every 12 hours, with a minimum of 6 hours between doses (for Cohort 1 pre-surgery abemaciclib should be taken as close to a 7AM – 7PM schedule as possible). Cycle length will be 28 days for all Cohort 2 cycles, even if treatment is held mid-cycle for toxicity. If a patient has not required dose reduction(s) due to toxicity during Cohort 2 Cycle 1, then the dose of abemaciclib may be escalated at the start of Cycle 2 to 200 mg every 12 hours if the investigator determines that it is in the best interest of the patient. Abemaciclib should be taken with or without food at approximately the same times each day with a glass of water and consumed over as short a time as possible. Participants should swallow the tablets as a whole. Abemaciclib tablets should not be opened, crushed, or chewed. Participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pomelos and exotic citrus fruits from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A4 interaction.

Instructions, including missed dose policy are included in the participant pill diary (Appendix E & F).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires an abemaciclib dose delay of > 28 days from the previous dose, the participant must be discontinued from treatment completely. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall P.I. Eudocia Quant Lee, MD (617-632-2166). Expected toxicities and dose reductions and modifications are detailed in Section 6.

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

Missed doses should be taken immediately when the participant realizes the dose was missed. Although doses should ideally be 12 hours apart, a minimum of 6 hours is allowed between doses in case of a missed dose. If the participant forgets to take his/her abemaciclib dose more than 6 hours from the normally scheduled dosing time (i.e., less than 6 hours to the time of the next planned dose), then that dose should be withheld and abemaciclib should be restarted at the time of the next planned dose.

Participants will keep a medication diary (see Appendix E & F). At the end of each cycle for Cohort 2 participants and after surgery for Cohort 1 participants, the diary will be returned and a new one will be given to the participant if continuing on therapy. Participants are to return all pill bottles and unused pills.

5.2 Cohort 1—Surgery Arm

In Cohort 1, 15-20 eligible participants who require reoperation will be treated with abemaciclib for 10-14 days prior to surgery. The last dose should be on the day of surgery and taken 1-3 hours prior to surgery and tumor removal. Since participants in cohort 1 are undergoing PK testing, accurately recording the time of study drug administration on day of surgery and recording the time of tumor removal are especially important and required.

In general, pre-operative, operative, and post-operative evaluations will consist of standard clinical practice. Required evaluations and research samples are detailed in Section 10.

After surgery on study, cohort 1 participants will come off study treatment and pursue standard cancer treatments as per the treating physician's discretion. Participants who enrolled on the surgical cohort before the surgical cohort was converted into a Phase 0, who have already started post-surgical abemaciclib dosing, and are benefitting from post-surgical abemaciclib treatment may remain on abemaciclib at the discretion of their treating physician and the approval of the overall PI, Dr. Eudocia Lee. These patients should instead follow the Study Calendar intended for Cohort 2 (nonsurgical) patients and their post-surgical C1D1 will represent C1D1 on the Cohort 2 study calendar.

Following registration, Cohort 1 pre-surgical Day 1 subjects should be evaluated for eligibility to treat based upon dose modification criteria outlined in Table 6.3 and not General Eligibility Criteria outlined here in Protocol Section 3; General Eligibility Criteria outlined here in Protocol Section 3 need only be met during screening for trial.

The goal is to have 15 eligible patients with adequate tissue for assessment of the primary objectives for this cohort. If sufficient tissue is not obtained for a patient enrolled in this cohort, the patient should continue treatment as originally intended and the clinical results reported. However, additional patients will be added to the cohort for the purpose of meeting the objectives related to tissue analysis. A maximum of 20 patients may be enrolled in this cohort. If the number of patients required to be replaced exceeds 5 consideration will be given to stopping enrollment to this cohort based on lack of feasibility.

5.3 Cohort 2—Treatment Arm

Participants will be treated with abemaciclib every 12 hours until tumor progression or unacceptable toxicity. Cycle length will be 28 days, even if treatment is held mid-cycle for toxicity. Criteria for dose modifications and delays apply to intra-cycle administration and day 1 administrations; there are no separate 'start of cycle' criteria; however Day 1 evaluations must be completed (and reviewed) before administration of study drug for that cycle (including C1D1). If a participant requires an abemaciclib dose delay of > 28 days from the previous dose, the participant must be discontinued from treatment completely. In exceptional cases where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall P.I. Eudocia Quant Lee, MD (617-632-2166).

In general, participants will be required to come to clinic at the start of each cycle. Required evaluations and research samples are detailed in Section 10.

5.4 General Concomitant Medication and Supportive Care Guidelines

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken from date of consent up to 30-day post drug study visit (as detailed in Section 10) should be recorded. If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the drug/therapy should be recorded.

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

5.4.1 Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

- Avoid concomitant use of CYP3A inducers and consider alternative agents.
- Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

5.4.2 Caution should be exercised when co-administering abemaciclib with narrow therapeutic drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A. Participants receiving such medications must be monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate. Please refer to Appendix D for a list of drugs. Please note that this list may not be comprehensive.

5.4.3 Abemaciclib is an inhibitor of P-gp; therefore, caution should be exercised when coadministering abemaciclib with P-gp substrate drugs with narrow therapeutic index (*e.g.*, digoxin). Abemaciclib may also inhibit the clearance of substrates of the renal transporter MATE1, such as endogenous creatinine and metformin.

5.4.4 Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Participants should stop using any herbal medications 7 days prior to first dose of study drug.

5.4.5 Corticosteroids should be used in the smallest possible dose to control symptoms of cerebral edema and mass effect, and discontinued if possible. Chronic dosing of corticosteroids is known to induce CYP3A enzymes, thereby increasing the risk of reducing abemaciclib drug exposure to sub-therapeutic levels.

NOTE for Cohort 1: every effort should be made to not exceed a corticosteroid dose of > 4 mg/day between date of registration and on-study surgery. If a corticosteroid of > 4 mg / day is necessary for a participant following registration and prior to on-study surgery, the treating investigator should reach out to the Overall PI, Dr. Eudocia Quant Lee, to confirm the participant's evaluability for tumor tissue studies.

5.4.6 Anti-seizure medications should be used as indicated. Only participants receiving non-EIAEDs are eligible. If for unavoidable clinical reasons (emergency department visit, severe allergies, toxicities, etc.) a participant's AED is switched to another AED, the following guidelines must be followed if applicable:

- Participants should be started on another non-EIAED if at all possible.
- Participants who are inadvertently and temporarily changed to an EIAED should immediately be changed to an alternative non-EIAED.
- Participants who need to permanently change anticonvulsant, but who cannot change to another non-EIAED, must be discussed with the PI.

5.4.7 Febrile neutropenia may be managed according to the local institution's guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the participant observed.

5.4.8 G-CSF: Routine prophylactic use of G-CSF is not permitted. However, therapeutic use in participants with serious neutropenic complications, such as sepsis, may be considered at the investigator's discretion.

5.4.9 Antiemetics: The use of antiemetics will be left to the investigators' discretion.

5.4.10 Pneumocystis jirovecii pneumonia (PJP) prophylaxis: Since participants with malignant gliomas are at increased risk of developing PJP, especially if they are on corticosteroids, prophylaxis for PJP may be considered per institutional practice.

5.4.11 Anticoagulants: Because of the potential for its interaction with study medications, warfarin sodium (Coumadin®), or any other coumadin-derivative anticoagulant, is not permitted at any dose. Low-molecular weight heparin and Xa inhibitors are permitted. If for unavoidable clinical reasons (emergency department visit, severe allergy, toxicity, etc) a participant is started on Coumadin, they must change to a low molecular weight heparin immediately in the interest of subject safety.

5.4.12 Surgery: If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the operative note, and pathology report.

5.4.13 Other Anticancer or Experimental Therapies: No other anticancer therapy of any kind is permitted during the study treatment period. No other drug under investigation may be used concomitantly with the study drug.

5.4.14 Radiotherapy: No radiotherapy of any kind is permitted during the study treatment period. Limited data are available with abemaciclib and radiotherapy or alternate dosing schedules (e.g. induction phase).

5.4.15 Other Concomitant Medications: Therapies considered necessary for the well-being of the participant may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

5.5 Criteria for Taking a Participant Off Protocol Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF).

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Dr. Eudocia Quant Lee, at 617-632-2166.

5.6 Duration of Follow Up

For all participants, off-treatment assessments are to be completed as described in Section 10.

A contact/visit to check for adverse events and vital status is to be performed at 30 days (+7 days) after the last study drug is given. This may be performed via documented phone conversation or in clinic with a study nurse or clinician. Content is further detailed in Section 10.

All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment or starting within 30 days of last study drug.

Participants who enter long-term follow-up will be followed via medical record review or contact (e.g., phone call) until death for post-treatment therapies, progression information, and survival. Each site will be responsible for collecting information on their participants regarding all post-treatment therapies, start and stop dates of those therapies, the reason for stopping those therapies, and the date of death.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with DF/HCC policy REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug. If administration of abemaciclib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 6.3.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the 30 day post-study visit (see section 10). Participants continuing to experience toxicity at the end-of treatment visits may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

All participants will be initially treated at Dose Level 0.

Table 6.0: Dose Levels

Dose Level	Dose of Abemaciclib
1*	200 mg every 12 hours
0 (starting dose)	150 mg every 12 hours
-1	100 mg every 12 hours
-2	50 mg every 12 hours
***If a patient has not required dose reduction(s) due to toxicity, then the dose of Abemaciclib may be escalated at the start of Cycle 2 to 200 mg every 12 hours if the investigator determines that it is in the best interest of the patient.	

6.1 Anticipated Toxicities

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

6.1.1 A list of adverse events of all grades suspected to be abemaciclib treatment related according to review of Investigator's Brochure, organized by CTCAE v4.0 category, includes:

- BLOOD & LYMPHATIC SYSTEM DISORDERS – White blood cell decreased, Neutrophil count decreased, Platelet count decreased, Anemia
- EYE DISORDERS – Cataract
- GASTROINTESTINAL – Diarrhea, Nausea, Vomiting, Dry mouth, Stomatitis
- GENERAL DISORDERS – Fatigue
- INFECTIONS & INFESTATIONS – Upper respiratory infection, lung infection, pharyngitis, urinary tract infection, conjunctivitis, sinusitis, vaginal infection, sepsis
- INVESTIGATIONS – Creatinine increased, Weight loss, Aspartate aminotransferase increased, Alanine aminotransferase increased, GGT increased
- METABOLISM & NUTRITION DISORDERS – Anorexia
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – Muscular weakness
- NERVOUS SYSTEM DISORDERS – Dysgeusia, Dizziness
- RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS – Pneumonitis
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Alopecia, Rash, Pruritis

- VASCULAR DISORDERS – Thromboembolic event

6.2 Dose Modifications/Delays

6.2.1 Table 6.3 should be adhered to for all toxicities considered at least possibly related to abemaciclib as noted below. If a participant experiences a toxicity unlikely or unrelated to treatment with abemaciclib but may still warrant a hold or reduction of study drug for safety, discussion and approval by Overall Principal Investigator and Study Sponsor, Eudocia Quant Lee, MD is recommended.

6.2.2 When treatment must be held pending resolution of toxicity to grade 1 or return to baseline, and the toxicity is a lab abnormality, in cases where participant had a pre-existing laboratory abnormality at baseline, the toxicity can be considered "resolved" from a hold perspective when it has resolved to within 1 grade of the baseline value. NOTE: For the purposes of data entry, values from screening assessments should be entered in as 'baseline' values. However, true "baseline values" - for the purpose of dose modifications on study, etc. - will be considered the last assessments/tests performed prior to initiation of study therapy.

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

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

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

6.2.5 No more than 2 levels of dose reduction are permitted in this study. Participants cannot be treated below dose level -2. If a participant whose abemaciclib dose has been reduced by 2 dose levels requires another dose reduction, treatment on study must be stopped unless the participant has benefited from the study, in which case the investigator will contact the overall Principal Investigator, Dr. Eudocia Quant Lee, to determine if the participant will remain in the study.

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

6.2.7 Dose re-escalation is never permitted in this study.

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

6.2.9 If study drug is held across a time point which requires collection of a research blood sample, please contact the Sponsor Coordinating Center or Overall PI (Dr. Eudocia Quant Lee) to confirm whether or not the sample should be collected or if the drug hold will negate the value of collection of the sample in question. If you anticipate the occurrence of such a scenario, please contact the Sponsor Coordinating Center as soon as possible in order to establish a plan prior to the time point in question.

6.2.10 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 6.3, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of abemaciclib. All SAEs must be reported as detailed in Section 7.4.

Table 6.3: Criteria for dose-modification and re-initiation of abemaciclib treatment

Table 6.3 should be adhered to for all toxicities considered at least possibly related to abemaciclib as noted below. If a participant experiences a toxicity unlikely or unrelated to treatment with abemaciclib but may still warrant a hold or reduction of study drug for safety, discussion and written approval by Overall Principal Investigator and Study Sponsor, Eudocia Quant Lee, MD is recommended.

Toxicity (organized per CTCAE v 4.0)	Actions
Investigations (for hyperglycemia, see *metabolism disorders*) *Unless otherwise specified, during duration of toxicity.*	

General Guidance for Hepatic Monitoring

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT 5×ULN and elevated TBL 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Hepatic Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	**Anti-actin antibody**
GGT	**Anti-smooth muscle antibody**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Reflex/confirmation dependent on regulatory requirements and/or testing availability.

ALT/SGPT or AST/SGOT - Grade 2 (>3.0- 5.0 x ULN) WITHOUT increase in total bilirubin above 2 x ULN	First Occurrence: Interrupt until resolution to ≤ grade 1, then • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolution to ≤ grade 1 takes > 7 days, resume ABEMACICLIB at one lower dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level

ALT/SGPT or AST/SGOT - Grade 3 (> 5.0 - 20.0 x ULN)	First Occurrence: Interrupt until resolution to ≤ grade 1, then • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolution to ≤ grade 1 takes > 7 days, resume ABEMACICLIB at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication. Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication.
ALT/SGPT or AST/SGOT - Grade 3 (> 5.0 - 20.0 x ULN) <u>WITH</u> increase in total bilirubin above 2 x ULN in the absence of cholestasis	Discontinue abemaciclib.
ALT/SGPT or AST/SGOT - Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.	
Creatinine **- Grade 2 (>1.5 - 3 x ULN)**	Maintain treatment with ABEMACICLIB
Creatinine **- Grade 3 (> 3.0 - 6.0 x ULN) if believed deterioration of renal function is suspected (as evidenced by changes in other markers of renal function, such as BUN, cystatin C, or calculated GFR based on cystatin C).**	Interrupt treatment until resolution to ≤ grade 1 or returned to baseline, treatment may resume at the same dose level or a 1 dose level decrease, at the investigator's discretion. Continuation of ABEMACICLIB is permitted upon recovery to stable Grade 2 if the investigator and overall principal investigator (Dr. Eudocia Quant Lee) agree that the event is not considered clinically significant.
Creatinine **- Grade 4 (> 6.0 x ULN) if believed deterioration of renal function is suspected (as evidenced by changes in other markers of renal function, such as BUN, cystatin C, or calculated GFR based on cystatin C)**	Discontinue ABEMACICLIB
General Guidance for Hematology Toxicity and Dose Modification Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib. Patients should be monitored closely for signs of infection, anemia, and bleeding.	
Anemia **- Grade 3 (Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated)**	First Occurrence: Interrupt until resolved to ≤ grade 2, then resume ABEMACICLIB at the current dose level Second Occurrence: Interrupt until resolution to ≤ grade 2, then resume ABEMACICLIB at one lower dose level
Anemia **- Grade 4 (Life-threatening consequences; urgent intervention indicated)**	Interrupt until resolution to ≤ grade 2, then resume ABEMACICLIB at one lower dose level

Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.
Neutropenia **- Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)**	First Occurrence: Interrupt until resolved to ≤ grade 2, then resume ABEMACICLIB at the current dose level Second Occurrence: Interrupt until resolution to ≤ grade 2, then resume ABEMACICLIB at one lower dose level
Neutropenia **- Grade 4 (ANC < 0.5 x 10^9/L)**	Interrupt until resolution to ≤ grade 2, then resume ABEMACICLIB at one lower dose level
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.
Thrombocytopenia **- Grade 3 (<50-25 x 10^9/L PLT)**	First Occurrence: Interrupt until resolved to ≤ grade 2, then resume ABEMACICLIB at the current dose level Second Occurrence: Interrupt until resolution to ≤ grade 2, then resume ABEMACICLIB at one lower dose level
Thrombocytopenia **- Grade 4 (PLT < 25 x 10^9/L)**	Interrupt until resolved to ≤ grade 2, then resume ABEMACICLIB at one lower dose level
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.
Gastrointestinal Disorders	
Guidelines for Diarrhea Management Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Our experience indicates early identification and intervention for the management of diarrhea has been helpful to patients. At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following: • At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow up. • Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day). • Site personnel should assess response within 24 hours.	

Diarrhea **- Grade 2 (4-6 stools/day > pretx)**	If diarrhea can be controlled with optimal anti-diarrheal treatment within 24 hours to either baseline or grade 1, continue ABEMACICLIB. If not, interrupt treatment until resolved to ≤ grade 1, then resume ABEMACICLIB at the current dose (treating investigators may reduce by 1 dose level at their own discretion for first occurrence). If diarrhea persists or returns as ≥ grade 2, then interrupt treatment until resolved to ≤ grade 1, then resume ABEMACICLIB at one lower dose level.
Diarrhea **- Grade 3 (7-9 stools/day > pretx)** **- Grade 4 (≥ 10 stools/day > pretx)** **(requires hospitalization)**	If diarrhea can be controlled with optimal anti-diarrheal treatment within 24 hours to either baseline or grade 1, continue ABEMACICLIB. If not, for diarrhea ≥ Grade 3 or requires hospitalization, interrupt treatment until resolved to ≤ grade 1, then resume ABEMACICLIB at one lower dose level.
Respiratory, Thoracic, and Mediastinal Disorders	
General Guidance for Interstitial lung disease (ILD)/Pneumonitis events Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported. Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask patients to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, cough, dyspnea, or interstitial infliltrates on radiologic exams.; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high resolution computer tomography (HRCT), broncheoalveolar lavage (BAL), and biopsy as clinically indicated (see also Table 7: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).	
Grade 1 or 2	Maintain treatment with ABEMACICLIB
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Interrupt until resolution to ≤ grade 1 or baseline, then resume ABEMACICLIB at one lower dose level
Grade 3 or 4	Discontinue ABEMACICLIB
Other unspecified RELATED adverse events	
Other unspecified Grade 1 and 2 events considered at least possibly related to ABEMACICLIB	Maintain treatment with ABEMACICLIB
Other unspecified persistent or recurrent Grade 2 events	Interrupt until resolution to ≤ grade 1 or baseline, then resume ABEMACICLIB at one lower dose level

considered at least possibly related to ABEMACICLIB that dose not resolve with maximal supportive measures within 7 days to baseline or Grade 1	
Other unspecified Grade 3 or 4 events considered at least possibly related to ABEMACICLIB	Interrupt treatment until resolution to ≤ grade 1 or baseline, then resume ABEMACICLIB at one lower dose level. Continuation of ABEMACICLIB is permitted upon recovery to stable Grade 2 if the investigator and overall principal investigator (Dr. Eudocia Quant Lee) agree that the event is not considered clinically significant.
Other unspecified UNRELATED adverse events	
Other unspecified events of any grade considered unlikely to be related or not related to study drug.	Maintain treatment with ABEMACICLIB. Interruption of ABEMACICLIB is permitted at the treating investigator's discretion. It is recommended that the investigator consults with the overall principal investigator (Dr. Eudocia Quant Lee) to determine that this is in the interest of the participant.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.2) and the characteristics of an observed AE (Section 7.3) will determine whether the event requires expedited reporting **in addition** to routine reporting in the study specific database.

7.1 General Information and Periods of Observation, Recording and Reporting

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or mother means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and recorded from the first dose of study treatment until 30 days after the last dose of study medication. The period for collection and recording of adverse events is extended for participants with ongoing reportable adverse events (protocol section 7.4) at least possibly related to study agent; for such participants, adverse events will be followed until the reportable event has resolved, stabilized, or determined to be irreversible by the reporting investigator. The Coordinating Center should be consulted prior to ending the follow-up of events that have stabilized.

7.1.1 Definitions

7.1.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after beginning study treatment, even

if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

7.1.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction with hypothetically might have caused death had it occurred in a more severe form)
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or,
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in participant hospitalization, or the development of drug dependency or drug abuse.

7.2 Expected Toxicities

7.2.1 Adverse Events List(s)

7.2.1.1 Adverse Event List(s) for Abemaciclib

Expected adverse events are those that have been previously identified as resulting from administration of the agent. **For the purposes of this study, an adverse event is considered <u>expected</u> when it appears in the Anticipated Toxicities list (protocol section 6.1.1) which is derived from the Investigator's Brochure.**

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access

to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.4.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities (unless specifically listed in this protocol as not requiring reported), and all grade 5 (death) regardless of study phase or attribution.

7.4.3 **Expedited Reporting Guidelines to DFCI Coordinating Center & Lilly**

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy. Other investigative sites outside of DF/HCC will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the AE form should be forwarded to the Overall PI within the timeframes detailed in the table below. The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.
In addition to local IRB reporting policies, all sites are required to following the below expedited reportable AE requirements:

Adverse Event Characteristics				**Reporting Requirement**	
Serious-ness	**Toxicity**	**Known Correlation[f]**	**Attribution to Abemaciclib**	**Eli Lilly and Company - Via Email[c] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**	**Overall PI (Eudocia Lee, MD) at the DFCI Coordinating Center Via Email [b] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**
Serious[e]	Any	Any (Expected or Unexpected)	Any	Within 15 business days from notification [a]	Within 24 hours from notification [a]
Non-Serious	Grade 4	Unexpected	Any	Not Required	Within 5 calendar days from notification [a]
Non-Serious	Grade 2 or 3	Unexpected	Possible, Probable, or Definite	Not Required	Within 5 calendar days from notification [a]

a. In the event that the participating investigator/site team does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator/site team is to report the event within required hours/days noted above after learning of it and document the time of his or her first awareness of the adverse event.
b. Email the Medwatch 3500A form, reportable AE coversheet (Appendix C), and the local IRB SAE report (if applicable) to the DFCI Coordinating Site with the subject title as "Abemaciclib SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Eudocia Quant Lee, and to the DFCI Coordinating Center personnel.
c. Reportable AE Coversheet is found in Appendix C. The coversheet contains all e-mails and needed for reporting purposes.
d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm
e. Seriousness is defined in section 7.1.1.2
f. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Anticipated Toxicities list (protocol section 6.1.1) which is derived from the Investigator's Brochure.

7.4.4 How to report AEs to Lilly & DFCI Coordinating Center/Overall PI

1. Document/describe AE on each of the following:
    a. MedWatch 3500A
        i. downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. DFCI Coordinating Center Reportable AE Coversheet
        i. AE Coversheet is found in Appendix C. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.

2. To report to DFCI Coordinating Center/Overall PI
    a. Scan and email completed Reportable AE Coversheet and MedWatch to NeuroOnc_SAE@dfci.harvard.edu with the subject title as "Abemaciclib SAE"
    b. All AE reports received at this account are forwarded immediately to the Overall PI (Dr. Eudocia Quant Lee), and to DFCI Coordinating Center personnel
    c. If available and applicable, please also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.

3. To report to Eli Lilly and Company
    a. Scan and email completed Reportable AE Coversheet and MedWatch to MAILINDATA_GSMTINDY@LILLY.COM and copy the DFCI Coordinating Center (NeuroOnc_SAE@dfci.harvard.edu)

NOTE: When reporting events to both Eli Lilly and DFCI, one e-mail can be sent to all parties simultaneously.

7.4.5 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

Events **not** considered to be serious adverse events for this protocol are:

- Lymphopenia (grade 2-4)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures (including off-treatment hospitalization for re-resection within 30-days of last dose of study drug to treat progressive disease)
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen since beginning study drug
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Hospitalization for seizure, related to GBM (disease under study) and unlikely/unrelated to study treatment

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

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

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 6.1.1.

8.1 Abemaciclib

8.1.1 Description

The chemical name is: [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine. Abemaciclib is also known as LY2835219 and is a selective, potent small molecule CDK4/6 dual inhibitor. The molecular weight is 506.60.

In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 17 to 38 hours. Following oral administration, abemaciclib was extensively metabolized followed by biliary excretion of metabolites. Strong CYP3A inhibitors may increase abemaciclib exposures, and strong inducers may decrease abemaciclib exposures. Caution should be exercised when coadministering abemaciclib with narrow therapeutic drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A.

8.1.2 Form

Abemaciclib drug product will be supplied for clinical trial use as abemaciclib with excipients in tablets. The drug products are stable when stored according to instructions

on the label.

50 mg Abemaciclib tablets will be supplied as a modified oval, immediate-release, aqueous, film-coated abemaciclib tablet containing 50 mg of abemaciclib and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, silicon dioxide, sodium stearyl fumarate, and color mixture beige.

8.1.3 Storage and Stability

Abemaciclib is stable when stored according to the instructions on the label.

8.1.4 Compatibility

There are no known compatibility issues.

8.1.5 Handling

Routine chemotherapy handling is recommended.

8.1.6 Availability

Abemaciclib is an investigation agent and will be supplied free-of-charge from Lilly Pharmaceuticals.

8.1.7 Preparation

None

8.1.8 Administration

- Abemaciclib will be administered at a starting dose of 150 mg every 12 hours. If a patient has not required dose reduction(s) due to toxicity, then the dose of Abemaciclib may be escalated at the start of Cycle 2 to 200 mg every 12 hours if the investigator determines that it is in the best interest of the patient. Doses should be spaced approximately 12 hours apart, with a minimum of 6 hours between doses. Abemaciclib should be taken with or without food at approximately the same times each day with a glass of water.. Participants should be instructed to take their doses, twice a day, at approximately the same times each day and approximately 12 apart (for Cohort 1 pre-surgery abemaciclib should be taken as close to a 7AM – 7PM schedule as possible), except on the days of the pharmacokinetic sampling at which time the participant should be instructed to not take their morning abemaciclib dose until after their clinic visit. For Cohort 1 pre-surgery abemaciclib, the last dose should be on the day of surgery 1-3 hours prior to surgery and tumor removal. Since participants in Cohort 1 are undergoing PK testing, accurately recording the time of study drug

administration on day of surgery and recording the time of tumor removal is especially important.

- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.
- If the participant forgets to take his/her abemaciclib dose more than 6 hours from the participant's normally scheduled dosing time (i.e., less than 6 hours to the time of the next planned dose), then that dose should be withheld and abemaciclib should be restarted at the time of the next planned dose.

8.1.9 Ordering

Drug supply will be ordered from Eli Lilly by site pharmacy personnel. A form, with drug information and email address for submission, will be supplied to each institution's pharmacy by the coordinating center once local IRB approval is received. Anticipate 3-5 business days to receive drug after the order is placed.

8.1.10 Accountability

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

8.1.11 Destruction and Return

Abemaciclib will be destroyed on site according to institutional policies, documented in the Drug Accountability Record Form. At the time of expiration / study close, a drug disposition form provided by *Lilly Pharmaceuticals Inc.* will be sent out to be signed off by the Pharmacist and Investigator verifying the destruction of drug.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Several biomarker and correlative studies are planned for this study.

9.1 Biomarker Studies from Any Prior Surgery

Eligibility for registration will be dependent on prior tumor being profiled by genomic methods that are sufficient for determination of the copy and mutation status of CDKN2A/B/C, RB1, and CDK4/6. Data can be generated from any prior tumor surgery. This data will not be generated as part of the trial process but will be pre-existing data. All data must be performed in a CLIA-certified laboratory. Central molecular pathology review will be performed and may include reports or raw data as needed to determine the status of relevant loci. Commonly used tests include:

1. OncoCopy Whole Genome Array CGH (DFCI/BWH)
2. OncoPanel Targeted Exome Sequencing (DFCI/BWH)
3. FoundationOne testing (Foundation Medicine)
4. Other sequencing and copy data (e.g. TGEN)
5. IMPACT sequencing and copy (MSKCC)

Data will be evaluated for:

1. Presence of CDKN2A, CDKN2B, CDKN2C loss equivalent to a loss greater than 1 copy of any one or more of these genes. Entry based on single copy loss will be allowed only in the event of a concurrent SNV present which is deemed likely damaging/inactivating by literature and database review.

AND

2. Absence of any copy, SNV, indel, or other aberration deemed likely inactivating in the RB1 gene. These would include non-sense mutations with truncation of protein, or homozygous (>1 copy) loss by copy analysis.

9.2 Laboratory Correlative Studies

Correlative studies and tissue required for these are mandatory for all participants with the exception of specified imaging studies.

Correlative study time points are included in Section 10 (Required Activity Calendar).

NOTE: Study Sponsor, or his/her designee, may ultimately opt to not pursue analysis of one or more of the correlative studies specified in the protocol if the study is not positive and/or the data gained from the analysis is no longer believed to be helpful.

Cohort 1: In this cohort, patients with recurrent GBM will receive drug for 10-14 days prior surgery, abemaciclib should be taken as close to a 7AM – 7PM schedule as possible during pre-

surgery cycle. The last dose should be on the day of surgery 1-3 hours prior to surgery and tumor removal.

During surgery, tumor tissue and plasma will be collected simultaneously. Planned analyses for resected tumor tissue as follows:

1) Frozen tumor samples and plasma samples will be evaluated for drug concentration using liquid chromatography - tandem mass spectrometry (LC-MS/MS) to derive a tumor/plasma ratio. Tumor concentration will be compared to plasma drug concentrations to determine if therapeutic levels of abemaciclib can be achieved in both enhancing and non-enhancing tumor.

2) Frozen tumor samples, archival and study surgery FFPE tumor tissue will be evaluated for drug target pathway dysfunction and for pharmacodynamic alterations of signal transduction molecules relevant to the response to abemaciclib. Tumor tissue will be analyzed by IHC and proteomics studies for pRb (S807/811), proliferation (e.g. Ki-67), and apoptosis (e.g. cleaved caspase 3) to determine if abemaciclib can achieve a pharmacodynamic effect in enhancing and non-enhancing tumor tissue. These data will be compared to similar analyses performed on tumor tissue not exposed to abemaciclib obtained from each participant's prior surgery, and from tumor specimens from untreated glioblastoma patients who undergo reoperation as part of another ongoing study (ABTC 1301: MLN0128 in recurrent glioblastoma).

3) Fresh-preserved tumor tissue and/or whole blood will be evaluated for the drug's immunostimulatory effects based on the following immunological assays:
    - TIL Density and TCR Overlap: We will evaluate whether next generation sequencing of the T cell receptor (TCR) repertoire within GBM tissue and blood can identify shared TCRs, which can then effectively track anti-tumor immune responses induced by abemaciclib. Genomic DNA will be isolated from fresh-frozen tumor (protocol surgery) and peripheral blood (immune monitoring timepoints) and subjected to next generation sequencing through the TCRVβ region to quantify TIL density and assess the overlap between tumor and peripheral blood. The TIL density and TCR overlap will then be correlated with clinical variables to identify potential biomarkers with prognostic and predictive value for outcomes (ORR, PFS, OS and toxicity). The TIL density and TCR overlap will be performed at Adaptive Biotechnologies (Seattle, WA). Investigators at the UCLA Brain Tumor Immunology Research Laboratory will perform analysis. Guidance on peripheral blood collection, processing and shipping is provided in Table 9.2 below.
    - Immunological multiplex immunofluorescence (IF) measurements: a minimum of 10 FFPE unstained sections from the protocol surgery are to be submitted per Table 9.2 below. Multiplex IF will be performed to assess the proportion of tumor infiltrating lymphocytes (TIL) with PD-1 expression and delineation of PD-L1 expression on GFAP+ tumor cells versus myeloid cells (CD45+) within the tumor microenvironment.
    - Peripheral Blood Immunophenotyping: The absolute lymphocyte count and

proportion of specific lymphocyte subsets will be quantified at each time point. Using a mass cytometry (CyToF) antibody panel analysis, lymphocyte/leukocyte subsets, activation markers, and negative costimulatory molecules will be evaluated before and after administration of abemaciclib. Lineage markers for immune cell populations, activation markers, memory/antigen experience markers, and exhaustion markers will be stained with an established 24 antibody CyToF panel. Analysis will be done using CyToF Kit and Phenograph, and clusters subsequently downloaded as .fcs files for analysis using FloJo. CyToF analysis will be performed on PBMC obtained from Ficoll density gradient separation of whole blood. Blood draws for this testing will be done pre-treatment and on the day of surgery prior to dosing. Guidance on peripheral blood collection, processing and shipping is provided in Table 9.2 below.

- Gene expression signatures and somatic mutations: Tumor samples from the protocol surgery should be immersed in Allprotect tissue reagent solution (Qiagen) or RNA-later® reagent and shipped to the UCLA Brain Tumor Research Laboratory. Exome sequencing (tumor/PBMC) and RNA Seq will be performed at the UCLA GenoSeq Core facility and analyzed. We will assess the number of somatic mutations and potential neoantigens in each tumor using a new UCLA-developed pipeline (veraT) and this data will be correlated with clinical variables to identify potential biomarkers with prognostic and predictive value for outcomes (ORR, PFS, OS). We will also develop immune signatures with the sequencing data and evaluate whether the presence of a pre-existing immune signature can also be correlated with clinical variables.

4) Frozen tumor tissue from protocol surgery will be characterized using single-cell RNA-sequencing using the SMART-Seq2 protocol to analyze the transcriptional profile of tumor cells treated with abemaciclib, allowing us to identify differences in cellular programs in comparison to historical untreated controls. Single-cell suspensions from frozen will be sorted based on CD45 expression and markers of cell integrity and viability and sorted into 96-multiwell plates containing cell lysis buffer. We plan to bank 15 plates of CD45-negative (primarily malignant cells) and 5 plates of CD45+ (primarily immune) cells per specimen with this method.

5) FFPE tumor tissue from protocol surgery will be evaluated for tissue microenvironment using multiplexed IF. The goal is to determine the tumor's immunological state and the immune milieu of the tumor microenvironment with respect to MHC and other markers.

6) We will also perform additional novel PK determinations using Maldi Mass Spec methods developed by Dr. Nathalie Agar (DFCI/BWH), which will be performed on frozen surgical specimens with excess tissue not needed for conventional methods of PK determination.

7) We will attempt to establish patient derived cells (PDC), cell lines/xenografts (PDCL/PDX) from patients on treatment with the goal to compare effects of abemaciclib on models to the patient response.

Cohort 1 Tumor Tissue Designation

Please note that surgery should be performed Sunday-Thursday to accommodate overnight shipment of tissues designated for immunologic assay for receipt by UCLA Monday-Friday (as UCLA will not accept samples on Saturday or Sunday). Before shipping any samples, please confirm the lab's receiving availability.

Four tissue samples (each at least 200mg) of the tumor will be collected from the contrast-enhancing (CE) area of the tumor and placed into individual cryovials labeled 1 (CE-PK), 2 (CE-PD), 5 (CE-IM), and 6 (CE-RNA). If deemed medically safe and feasible, two additional tissue samples (each at least 200mg) will be collected from a non-contrast-enhancing (NCE) area of the tumor and placed into individual cryovials labeled 3 (NCE-PK) and 4 (NCE-PD).

The tubes labeled 1 (CE-PK) and 3 (NCE-PK) will be used for pharmacokinetic/drug concentration measurements. The tubes labeled 2 (CE-PD) and 4 (NCE-PD) will be used for pharmacodynamic protein analysis for determination of modulation of the targeted pathway, and/or for nucleic acid extraction and genomic analysis (array CGH, sequencing). The tube labeled 5 (CE-IM) will be used for immunologic correlatives. The tube labeled 6 (CE-RNA) will be used for transcriptional profiling via single-cell RNA-sequencing.

Every effort should be made to collect adequate amounts of tissue as this is a primary objective of the study. On average, each 200mg specimen should be approximately 0.5 cm^3 in volume (size of a large green pea). In the event of inadequate tissue to meet the minimum requirements, the maximum amount of tissue available should be collected and submitted within the tube labeled 1 (CE-PK) or 3 (NCE-PK).

Portions of the tissue should be analyzed by frozen section or smear preparation by a pathologist or designated assistant to confirm viability and presence of >50% tumor nuclei in the tissue samples submitted (<30% necrosis). Tissue viability will ultimately also be confirmed by the central neuropathology team at the DFCI Coordinating Center.

Once confirmed and allocated to the proper tubes, all tissue samples EXCEPT for the tubes labeled 5 (CE-IM) and 6 (CE-RNA) should be snap frozen and stored at the local site at -70 degrees Celsius or lower temperature until the local pathologist has finalized the clinical diagnosis and confirmed that tissue is no longer required for diagnosis. Tissue for the immunologic studies labeled 5 (CE-IM) should be fresh preserved tissue. Tissue labeled 6 (CE-RNA) should be frozen on dry ice without OCT or LN2.

If more tissue is available, an additional 200mg or larger sample should be sent fresh to the appropriate hospital research lab for establishment of a participant primary cell line (serum free, neurosphere methods) by the site's standard procedures. All remaining tissue from the resection should then be processed in a routine manner (formalin fixation and paraffin embedding) for clinical pathologic interpretation.

Both types of tissue (fresh tissue and FFPE) will be processed for correlative studies. Samples for tissue PK analysis should be sent to the Pharmacoanalytical Shared Resource, under the direction of Dr. Mitch Phelps at The Ohio State University (OSU). Samples for tissue PD analysis and tissue microenvironment should be sent to Dr. Keith Ligon at DFCI. Samples for immunologic assays should be sent to Dr. Robert Prins at UCLA.

Pharmacokinetic (PK) Samples:

Once local collection and analysis are complete, tissue samples for PK analysis [tubes labeled 1 (CE-PK), 3 (NCE-PK)] should be shipped to the address below approximately 30 days after surgery.

Preparing the shipment

E-mail the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu **at least 24 hours** prior to shipment of samples to confirm the receiving lab is aware of the shipment.

Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).

- Organize the samples by patient and timepoint in the box.
- Do not store in plastic bags (they break on dry-ice and labels will detach).
- A copy of each of the PK sample collection forms for the respective patients or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.
- Note the study number, PI, and the drugs used/to be measured.
- A name, phone number, and email address should be included with samples so that receipt can be acknowledged.

Shipping

- All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.
- Tissue PK samples should be sent on Monday through Wednesday (never on Thursday. Friday, weekends, or days prior to a holiday) to:

The OSUCCC Pharmacoanalytical Shared Resource
Attn: Kasey Hill, PhD
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, Ohio 43210
Phone: (614) 688-0578
Fax: (614) 292-7766
Email: PhASR@osumc.edu

Upon shipment, send a notification with tracking number to the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu and OSUCCC Pharmacoanalytical Shared Resource at PhASR@osumc.edu

Pharmacodynamic (PD), Tumor Microenvironment Samples, and Single-Cell RNA Sequencing Samples:

Once local collection and analysis are complete, tissue samples for PD analysis [tubes labeled 2 (CE-PD), 4 (NCE-PD)] and single-cell RNA sequencing [tube labeled 6 (CE-RNA)] as well as 10 slides from study surgery, and 20 slides from archived samples for PD and tumor multiplexed IF microenvironment analysis should be shipped to the central site (DFCI, Dr. Keith L. Ligon, JR McFaline-Figueroa, M Suva) within 30 days after surgery.

- Email the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu **at least 24 hours** prior to shipment of samples to confirm the receiving lab is aware of the shipment.
- A memorandum indicating the study, the date of submission, name of study site submitting the tissue, and a list of contents. The DFCI Coordinating Center will supply a template memorandum to sites at the time of the SIV or upon request.
- Include copy of the pathology and surgical reports for the sample being submitted

Samples should be sent on a Monday through Thursday (never on Friday, weekends, or days prior to a holiday) to:

Dr. Keith L. Ligon (attn.: Adult Path CRC)
Dana-Farber Cancer Institute
Center for Molecular Oncologic Pathology - JF215B
450 Brookline Ave
Boston, MA 02215
Ph 617-632-2357

Upon shipment, send a notification with tracking number to the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu

Immunologic Samples:

Samples for immunologic assays [fresh-preserved tumor tissue in tube labeled 5 (CE-IM), FFPE slides from the protocol surgery, archival FFPE slides from prior surgery, and whole blood] should be shipped via FedEX for overnight delivery directly to UCLA. Guidelines for submission of these immunologic samples as follows (please see Table 9.2 below for details):

- FFPE slides from archival tissue and protocol surgery should be cut and submitted when requested by the DFCI Coordinating Center, when study recruitment has ended. Ship slides in a plastic slide holder/slide box. Place a small wad of padding in top of the container in order to avoid slides breaking during shipping and handling process.
- Complete the provided UCLA Brain Tumor Research Lab memorandum indicating the study, subject ID assigned at registration, date of submission, name

of study site submitting the tissue, and a list of contents.

- The DFCI Neuro-Oncology Coordinating Center will provide supplemental Sample Collection & Shipping Guidance to sites at the time of activation or upon request.
- Include a copy of the pathology and surgical report for the sample(s) being submitted.
- Confirm the lab's receiving availability by checking the web calendar. All samples should be shipped via FedEx for overnight delivery to UCLA. On-study tissue & blood samples should be obtained Sunday-Thursday for a Monday-Friday arrival at UCLA. **UCLA is unable to accept samples on Saturday or Sundays.**
- An email is to be sent **before** each shipment to the UCLA Brain Tumor Research Lab at RPrinsLab@mednet.ucla.edu and the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu indicating what is being shipped and when.
- Please note that the submitting institution is responsible for the costs of shipping and handling.
- Ship samples to:

  Robert M. Prins, Ph.D. c/o Sylvia Odesa
  Gonda Research Lab, Room 1554
  695 Charles E. Young Drive South
  Los Angeles, CA 90095
  Telephone: 310-794-5663
  Email: RPrins@mednet.ucla.edu and SOdesa@mednet.ucla.edu

Upon shipment, send a notification with tracking number to the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu and UCLA at RPrins@mednet.ucla.edu

Table 9.2: Summary of Correlative Studies

Biomarker name (Lead PI and Site)	Cohort	Assay	Tissue/Body Fluid Tested and Timing of Assay	Collection and Packaging	Address to Send Sample
Tissue PK (M. Phelps, OSU)	Cohort 1	Liquid chromatography - tandem mass spectrometry (LC-MS/MS)	Fresh frozen tissue from protocol surgery (enhancing and non-enhancing tumor)	Protocol surgery: 200mg of fresh frozen tissue from the contrast-enhancing tumor placed into individual cryovial labeled 1 (CE-PK). If deemed medically safe and feasible, 200mg of fresh tissue from non-contrast-enhancing tumor and placed into individual cryovial labeled 3 (NCE-PK).	The OSUCCC Pharmacoanalytical Shared Resource Attn: Kasey Hill, PhD 441 Biomedical Research Tower 460 West 12th Avenue Columbus, Ohio 43210 Phone: (614) 688-0578 Fax: (614) 292-7766 Email: PhASR@osumc.edu
Plasma PK (M. Phelps, OSU)	Cohort 1	Liquid chromatography - tandem mass spectrometry (LC-MS/MS)	Peripheral blood (pre-treatment, D8, at tumor resection)	4mL blood should be collected (EDTA) prior to start of pre-surgery drug Day 1 (pre-dose), pre-surgery Day 8 (pre-dose), and on day of surgery at time of tumor resection. Plasma should be separated and collected in a cryotube (polypropylene cryovials Nunc) that can be snap frozen. Plasma PK cryotubes should be labeled with date drawn, time drawn, participant number & initials, and PK time point, then frozen at -70°C or below	The OSUCCC Pharmacoanalytical Shared Resource Attn: Kasey Hill, PhD 441 Biomedical Research Tower 460 West 12th Avenue Columbus, Ohio 43210 Phone: (614) 688-0578 Fax: (614) 292-7766 Email: PhASR@osumc.edu
Plasma PK (M. Phelps, OSU)	Cohort 2	Liquid chromatography - tandem mass spectrometry (LC-MS/MS)	Peripheral blood	4mL blood should be collected (EDTA) pre-dose at C1D1, C2D1, C3D1 and C4D1. Plasma should be separated and collected in a cryotube (polypropylene cryovials Nunc) that can be snap frozen. Plasma PK cryotubes should be labeled with date drawn, time drawn, participant number & initials, and PK time point, then frozen at -70°C or below	The OSUCCC Pharmacoanalytical Shared Resource Attn: Kasey Hill, PhD 441 Biomedical Research Tower 460 West 12th Avenue Columbus, Ohio 43210 Phone: (614) 688-0578 Fax: (614) 292-7766 Email: PhASR@osumc.edu

Tissue PD IHC, Proteomics, and Tumor microenvironment (K Ligon, DFCI; JR McFaline-Figueroa, DFCI)	Cohort 1	IHC for pRb (S807/811), proliferation, and apoptosis IF Multiplex for immune markers / antigen presentation	Archived FFPE tissue and fresh frozen tissue from protocol surgery	Archived: 20 unstained plus slides cut at 5um thickness Protocol surgery: 10 unstained slides cut at 5um thickness Protocol surgery: 200mg of fresh frozen tissue from the contrast-enhancing tumor placed into individual cryovial labeled 2 (CE-PD). If deemed medically safe and feasible, 200mg of fresh tissue from non-contrast-enhancing tumor and placed into individual cryovial labeled 4 (NCE-PD).	Dr. Keith L. Ligon (attn.: Adult Path CRC) Dana-Farber Cancer Institute Center for Molecular Oncologic Pathology - JF215B 450 Brookline Ave Boston, MA 02215 Phone 617-632-2357
TIL Density and TCR Overlap (R Prins/T Cloughesy/ L Liau, UCLA)	Cohort 1	TCR ImmunoSeq and TCR Overlap (Adaptive Biotech.) on tumor tissue and peripheral blood mononuclear cell genomic DNA	Fresh preserved tissue from protocol surgery and peripheral blood (pre- and post-treatment)	Protocol surgery: 200 mg of fresh tissue (approximately 20% tumor nuclei) sent in 2 mL Allprotect ® tissue reagent (Qiagen) or RNA-later® reagent and placed into an individual cryovial labeled 5 (CE-IM). Pre-treatment and post-treatment PBMC can be used from blood collected for peripheral blood immunophenotyping (see below)	Robert M. Prins, Ph.D. C/O Sylvia Odesa Gonda Research Lab, Room 1554 695 Charles E. Young Drive South Los Angeles, CA 90095 Phone: 310-794-5663
Immunologic IHC measurements (R Prins/T Clougesy/L Liau, UCLA)	Cohort 1	IF Multiplex for PD-1/PD-L1/CD8/CD4/CD8/CD6845/GFAP IHC on FFPE tumor tissue	Archived FFPE tissue and protocol surgery FFPE tissue	Slides are to be cut and submitted when requested by DFCI Coordinating Center. Archived: 7 FFPE unstained continuous 5 micron thick slides on Superfrost Plus glass slides from most recent surgery revealing glioblastoma Protocol surgery: 7 FFPE unstained continuous 5 micron thick slides on Superfrost Plus glass slides	Robert M. Prins, Ph.D. C/O Sylvia Odesa Gonda Research Lab, Room 1554 695 Charles E. Young Drive South Los Angeles, CA 90095 Phone: 310-794-5663
Peripheral Blood Immunopheno-typing (R Prins/ T Cloughesy/ L Liau, UCLA)	Cohort 1	Mass Cytometry on peripheral blood mononuclear cells	Peripheral blood (Pre-surgery pre-treatment, pre-surgery post - treatment)	Pre-surgery pre treatment blood: 10 Green top tubes (10ml/tube – sodium heparin tubes preferred) following registration/randomization and pre-abemaciclib Pre-surgery post treatment blood:10 Green top tubes (10ml – sodium heparin tubes preferred) prior to abemaciclib dosing on the morning of	Robert M. Prins, Ph.D. C/O Sylvia Odesa Gonda Research Lab, Room 1554 695 Charles E. Young Drive South Los Angeles, CA 90095 Phone: 310-794-5663

				surgery	
Gene expression signatures and somatic mutations (R Prins / T Cloughesy / L Liau, UCLA)	Cohort 1	RNA Seq on tumor gDNA/RNA	Fresh preserved tissue from protocol surgery and peripheral blood (pre- and post-treatment)	The protocol surgery sample labeled 5 (CE-IM). collected for TIL Density and TCR Overlap will also be used for gene expression signatures and somatic mutations. Pre-treatment and post-treatment PBMC can be used from blood collected for peripheral blood immunophenotyping (see above).	Robert M. Prins, Ph.D. C/O Sylvia Odesa Gonda Research Lab, Room 1554 695 Charles E. Young Drive South Los Angeles, CA 90095 Phone: 310-794-5663
Single-cell RNA-sequencing (M Suva, MGH)	Cohort 1	Single-cell RNA-sequencing (SMART-Seq2)	Frozen tissue from protocol surgery	Protocol surgery: 200mg of fresh frozen tissue (frozen on dry ice, no OCT, no LN2) < 3 hours from surgery, obtained from the contrast enhancing region and placed into an individual cryovial labeled 6 (CE-RNA).Freeze the tumor specimen (frozen on **dry ice**, no OCT, no LN2). 200 mg (~0.5cm^3) of tissue.	Dr. Keith L. Ligon (attn.: Adult Path CRC) Dana-Farber Cancer Institute Center for Molecular Oncologic Pathology - JF215B 450 Brookline Ave Boston, MA 02215 Phone 617-632-2357
Cell line studies (K Ligon, DFCI)	Cohort 1	Dynamic response to abemaciclib in vitro	Cell line derived from protocol surgery	Protocol surgery: 200mg or more tissue should be sent fresh to the local hospital research lab for establishment of a participant primary cell line (serum free, neurosphere methods) by the site's standard procedures. For sites that create cell lines locally the central site (DFCI, Dr. Keith L. Ligon) will request frozen aliquot of live cells in DMSO – if available – at a later date (may be ~ 6 months after surgery); but this is not a mandated study submission. If the local site does not have capability or would prefer the fresh tissue can be submitted in RMPI media to Dr. Ligon's lab for culture instead of the local site. This should be shipped at 4 degrees on wet ice.	Dr. Keith L. Ligon (attn.: Adult Path CRC) Dana-Farber Cancer Institute Center for Molecular Oncologic Pathology - JF215B 450 Brookline Ave Boston, MA 02215 Ph 617-632-2357

Cohort 1 Blood Samples for Peripheral Blood Immunophenotyping:

Ten Green top tubes (each 10ml/tube – sodium heparin tubes preferred) should be collected prior to the start of pre-surgery Day 1 (pre-dose) and prior to morning abemaciclib dose on day of surgery. Blood samples for immunologic assays should be shipped (along with the fresh-preserved tumor tissue) via FedEX for overnight delivery directly to UCLA as described in Table 9.2.

Cohorts 1 & 2 Plasma Pharmacokinetic (PK) Samples:

Cohort 1 Pre-Surgery/Surgery
4mL blood should be collected in purple-top EDTA vacutainer (Becton Dickinson Catalog # 367861 or 367844, Franklin Lakes, NJ) prior to start of pre-surgery Day 1 (pre-dose), pre-surgery Day 8 (pre-dose), and on day of surgery at time of tumor resection. All samples should be prior to morning abemaciclib dose.

Cohort 2
For all Cohort 2 participants, 4mL blood should be collected (in purple-top EDTA vacutainer (Becton Dickinson Catalog # 367861 or 367844, Franklin Lakes, NJ) at C1D1 (pre-treatment), C2D1, C3D1 and C4D1(if a participant comes off study treatment prior to C4D1 visit, then an end of treatment sample should be drawn). All samples should be prior to morning abemaciclib dose.

Handling of Specimen(s)

- Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis.
- Fill-up the tubes as much as possible until blood flow stops.
- GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis.
- Place samples immediately **on ice** after collection; samples must be processed **within 20 minutes**.

Processing instructions

1. Invert sample 8-10 times immediately before processing.
2. Place the sample(s) on ice or in a refrigerator and separate the **plasma within 60 minutes of collection** at 1,500 - 2,000 x g for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
3. Carefully remove tube from centrifuge.
4. Using a pipette, transfer equal aliquots of plasma into 2 labeled 2 mL cryovials, not exceeding 1.5 mL per cryovial.
5. Label samples as Abemaciclib PK, including protocol number (16-383), unique patient ID (assigned by the consortium), initials, date of collection, draw time, and time point.
6. Store plasma samples at -70ºC or below until shipment or transfer to OSU.

Plasma PKs will be batch shipped when requested by the DFCI Coordinating Center.

Preparing the shipment
E-mail the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu **at least 24 hours** prior to shipment of samples to confirm the receiving lab is aware of the shipment.

Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH).

- Organize the samples by patient and timepoint in the box.
- Do not store in plastic bags (they break on dry-ice and labels will detach).
- A copy of each of the PK sample collection forms for the respective patients or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet.
- Note the study number, PI, and the drugs used/to be measured.
- A name, phone number, and email address should be included with samples so that receipt can be acknowledged.

Shipping

- All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state.
- Tissue PK samples should be sent on Monday through Wednesday (never on Thursday. Friday, weekends, or days prior to a holiday) to:

The OSUCCC Pharmacoanalytical Shared Resource
Attn: Kasey Hill, PhD
441 Biomedical Research Tower
460 West 12th Avenue
Columbus, Ohio 43210
Phone: (614) 688-0578
Fax: (614) 292-7766
Email: PhASR@osumc.edu

Upon shipment, send a notification with tracking number to the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu and the OSUCCC Pharmacoanalytical Shared Resource at PhASR@osumc.edu

Archival Tissue Samples for Screening and Correlative Studies

Guidelines for submission of archival tumor tissue and for PD and tumor antigen presentation and microenvironment correlative studies at DFCI:

- A memorandum indicating the study, the date of submission, name of study site submitting the tissue, and a list of contents. The DFCI Coordinating Center will supply a template memorandum to sites at the time of the SIV or upon request.
- Include copy of the pathology, surgical, and genomic profiling/sequencing reports for the sample being submitted

- Email the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu **at least 24 hours** prior to shipment of samples to confirm the receiving lab is aware of the shipment.

  Samples should be sent on a Monday through Thursday (never on Friday, weekends, or days prior to a holiday) to:

  Dr. Keith L. Ligon (attn.: Adult Path CRC)
  Dana-Farber Cancer Institute
  Center for Molecular Oncologic Pathology - JF215B
  450 Brookline Ave
  Boston, MA 02215
  Ph 617-632-2357

  Upon shipment, send a notification with tracking number to the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu

Guidelines for submission of archival tumor tissue for immunologic correlative studies at UCLA:

- FFPE slides from archival tissue should be cut and submitted when requested by the DFCI Coordinating Center, when study recruitment has ended. Ship slides in a plastic slide holder/slide box. Place a small wad of padding in top of the container in order to avoid slides breaking during shipping and handling process.
- Complete the provided UCLA Brain Tumor Research Lab memorandum indicating the study, subject ID assigned at registration, date of submission, name of study site submitting the tissue, and a list of contents.
- The DFCI Neuro-Oncology Coordinating Center will provide supplemental Sample Collection & Shipping Guidance to sites at the time of activation or upon request.
- Include a copy of the pathology and surgical report for the sample being submitted
- An email is to be sent before each shipment to the UCLA Brain Tumor Research Lab at RPrinsLab@mednet.ucla.edu and the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu indicating what is being shipped and when.
- Please note that the submitting institution is responsible for the costs of shipping and handling.
- Ship slides to:
  Robert M. Prins, Ph.D.
  C/O Sylvia Odesa
  Gonda Research Lab, Room 1554
  695 Charles E. Young Drive South
  Los Angeles, CA 90095
  Telephone: 310-794-5663
  Email: RPrins@mednet.ucla.edu and SOdesa@mednet.ucla.edu

  Upon shipment, send a notification with tracking number to the DFCI Coordinating Center at NeuroOnc_Coor@dfci.harvard.edu and UCLA at RPrins@mednet.ucla.edu

9.2.1 DFCI/BWH Testing of Pre-Post Treatment Tumor Tissue

An example of the DFCI prescreening results that may be generated prior to trial entry is described below. In addition, all Cohort 1 on surgery samples will be tested post-treatment tissue using these same assays for comparison to pre-treatment tissue. DFCI FFPE tumor tissue from the participant's surgery prior to enrolling onto the study or Cohort 1 post-treatment tissue will be genotyped with the clinically validated OncoPanel targeted exome sequencing for 300 cancer causing genes and whole genome OncoCopy Agilent array comparative genomic hybridization at 1M probe resolution, and the results correlated with outcome. Both assays are performed in the CLIA-certified laboratory at the Dana-Farber/Brigham and Women's Cancer Center, Center for Advanced Molecular Diagnostics (CAMD).

9.2.1.1 OncoCopy Whole Genome Array CGH (DFCI/BWH)

Tissue requirements for aCGH are 10 x 5 μm standard formalin-fixed paraffin embedded (FFPE) tumor sections or 5 x 0.5 mm tissue cores containing at least 50% tumor nuclei and less than 10% necrosis. At least 1.3 u μg tumor DNA (nanodrop quantification) is required. As previously described, aCGH is performed using DNA fragmentation simulation methods (FSM) with Agilent SurePrint G3 1x1M arrays (Craig et al., 2012). Whole genome data are generated and analyzed using proprietary cytogenomics software. Copy number aberrations (CNAs) are curated to prioritize genetic events most likely to have diagnostic, prognostic and/or therapeutic significance in brain tumors in order to generate a genotyping list of at least 40 different genomic imbalances. The time required from tissue submission to data reporting averages two weeks or less. A distinct advantage of this assay is that whole genome data may be reanalyzed at later time points or in exploratory arms of the study without additional cost. In addition, the use of a dedicated and robust copy number assay whose performance is well characterized allows for inclusion of more reproducible results in future studies.

9.2.2 OncoPanel Targeted Exome Sequencing (DFCI/BWH)

DNA will be isolated from 5-10 5 μm FFPE slides or 3 x 0.6 mm tissue cores, frozen tissue or genomic DNA from a CLIA lab containing at least 50% tumor nuclei using routine extraction methods previously described (Wagle et al., 2012). At least 200ng of genomic dsDNA is required (PicoGreen quantification). Somatic mutations in tumor DNA will be detected using the high-throughput targeted deep sequencing OncoPanel in the DF/BWCC CLIA-certified laboratory at the Brigham and Women's Hospital (Center for Advanced Molecular Diagnostics-CAMD, Molecular Pathology Dr. Neal Lindeman, Director). Briefly, massively parallel sequencing libraries (Illumina) that contain barcoded universal primers will be generated using genomic DNA from FFPE tumor material to be used in solution-phase hybrid capture with biotinylated RNA baits. Sequencing data is analyzed for single nucleotide sequence variants, small insertions/deletions, and DNA copy-number alterations in exons from 275 actionable cancer genes including oncogenes and tumor suppressors.

9.2.3 Immunohistochemistry Correlates for Cohort 1 Patients

Tumor from all patients will be evaluated by IHC for PD (including the levels of pRB1, CC3, Ki67, and other markers of abemaciclib), tumor microenvironment, as well as immunologic changes in pre or pre-post treatment pairs. These studies will require a total of 17 IHC unstained plus slides cut at 5um thickness (Cohort 1 and 2, archived and study surgery). Ten slides should be sent to Dr. Keith Ligon at DFCI and 7 slides (on Superfrost Plus glass slides) should be sent to Dr. Robert Prins at UCLA. This is for correlation only and is not utilized for trial entry/screening.

9.3 Special Studies

Cell Line Sample:

Primary glioblastoma patient derived cell lines (PDCLs) derived from glioblastoma participants have been shown to retain key genetic and expression characteristics of the parent tumor and offer a potentially advantageous exploratory mechanism for biologic analysis of response in individual participant tumors as well as potential diagnostic predictor of participant response to drug. Primary glioblastoma cell lines develop successfully from roughly half of all attempts at culturing. Attempted culturing of PDCLs is expected for all Cohort I surgeries. In addition, for participants who are also enrolled in the Ivy Stage 0 tissue banking protocol, cells lines established at new diagnosis may be available. As such we will seek to study and compare responses to abemaciclib in any participant cell lines which are derived by participating sites from newly diagnosed or treated participant specimens at recurrence. Cell lines will be studied for the dynamic response to abemaciclib in vitro as read out by similar IHC, Western, and pharmacodynamic measures described for tissue samples above (e.g., pRb reduction, KI-67 measurement of proliferation index). These studies will be coordinated or performed by the laboratory of Dr. Keith Ligon at DFCI.

To achieve a cell line, an additional sample (200mg size of green pea or larger) should be sent fresh to the local hospital research lab for establishment of a participant primary cell line (serum free, neurosphere methods) by the site's standard procedures. If the local site does not have capability or would prefer the fresh tissue can be submitted in RMPI media to Dr. Ligon's lab for culture instead of the local site. This should be shipped at 4 degrees on wet ice. All cell lines derived from the study participants will be shared with the site of referral. For sites that create cell lines locally the central site (DFCI, Dr. Keith L. Ligon) will request frozen aliquot of live cells in DMSO – if available – at a later date (may be ~ 6 months after surgery); but this is not a mandated study submission.

10. STUDY CALENDAR

Table 10 describes required procedures. All procedures may increase in frequency if clinically indicated or oriented following a toxicity/adverse event.

Table 10.1 Required Activity Calendar for Cohort 1 only

Examination	Screening[a]	Pre-Surgery		During Surgery[d]	Post-Surgery[e]	30-Day Post Drug[f]
		D1[b]	D8[c]			
Informed consent[g]	X					
Background Information	X					
Inclusion/Exclusion Criteria[h]	X					
Serum Pregnancy Test[i]	X	X				
Vital Signs[j]	X					
Neuro & Physical Exam	X					
KPS[k]	X					X
Con-Med & Adverse Event Assessments l		----------X----------				
12-lead ECG	X					
Imaging – MRI[m]	X					
Hematology[n]	X	X	X			
Serum Chemistry[o]	X	X	X			
Coagulation (PT/INR, PT, PTT)	X					
Submission of Archival Tissue[p]	X					
Blood for Immunophenotyping[q]		X		X		
Plasma PK Collection[r]		X	X	X		
Tumor Resection[s]				X		
Abemaciclib Administration[t]		Every 12 hours including morning of surgery		*none*		

a. To be performed within 14 days of registration unless specified otherwise.

b. Pre-surgery Day 1 assessments to be performed within 3 days prior to drug day 1 unless specified otherwise.

c. Pre-surgery Day 8 assessments to be performed within +/- 1 day.

d. Surgery to occur after participant is on daily drug for 10-14 days. Abemaciclib is to be taken on the morning of/before the surgery 1-3 hours prior to surgery and tumor removal. Since participants in cohort 1 are undergoing PK testing, accurately regarding the time of study drug administration on day of surgery and recording the time of tumor removal are especially required. Procedures to be documented during surgery, and samples to be collected, are detailed in section 9.

e. Post-surgery period is the time following surgery. No protocol specific assessments are required for this period; sites may obtain assessments as clinically indicated.

f. A contact/visit for review of concomitant medications, adverse events, and KPS (no neurologic exam required at 30-day FU time point) is to be performed at 30 days + 7 days after the last study drug is given. This may be performed via documented phone conversation with a study nurse or clinician. All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment or starting within 30 days of last study drug

g. Per DF/HCC multi-center policy, must be obtained by MD attending. Informed Consent may be performed up to 28 days prior to registration Per DF/HCC multi-center policy, must be obtained by MD attending. Informed Consent may be performed up to 28 days prior to registration.

h. Please see section 3. Genomic profiling data from previously performed sequencing and/or copy number array data to verify status of CDKN2A/B/C and RB1 must be available prior to registration.

i. Serum pregnancy test only for women of child bearing potential (as defined in Section 3.1.20). Serum pregnancy test within 7 days prior to Day 1 drug for registration purposes and repeated within 72 hours prior to Day 1 drug if original screening pregnancy test is not within 72 hours of Day 1 drug.

j. Vital signs: Weight, heart rate, blood pressure, respiration rate, temp. Height required only at baseline (any height within 1 year of registration is acceptable).

k. Karnofsky Performance Status (KPS)

l. Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator. Concomitant medications and reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.

m. Imaging: gadolinium-enhanced contrast and non-contrast MRI. CT alternative, if MRI contraindicated. When feasible at a site, appendix G MRI Acquisition Protocol should be adhered to.Imaging: gadolinium-enhanced contrast and non-contrast MRI. CT alternative, if MRI contraindicated. When feasible at a site, appendix G MRI Acquisition Protocol should be adhered to and the same imaging technique should be used in a participant throughout the trial. Screening baseline scan within 14 days prior to registration.

n. Hematology – erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)Hematology – erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

o. Biochemistry - albumin, alkaline phosphatase (ALP), bicarbonate (HCO_3), BUN, calcium, chloride, creatinine, glucose, magnesium, phosphorous, potassium, SGOT (AST), SGPT (ALT), sodium, total protein, total bilirubin, amylase and lipase, LDH and uric acid. If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed.

   Coagulation assays of PT/INR, PT, PTT required at screening only.

p. Archival tumor tissue per eligibility point 3.1.11 must be submitted to the DFCI Coordinating Center within 60 days of registration.

q. Required at pre surgery C1D1 (pre-dose) and prior to the morning dose on the day of surgery.

r. Required at pre surgery C1D1 (pre-dose), pre-surgery Day 8 (pre-dose), and day of surgery at the time of tumor resection for Cohort 1 participants.

s. See section 9 for details on tumor tissue requirements. On-study surgery tissue should be submitted within 60 days of date of surgery.

t. Please see protocol section 8.1.8 for abemaciclib administration instructions

Table 10.2 Required Activity Calendar for Cohort 2 only

Examination	Screening[a]	Cycle 1 D1[b]	Cycle 1 D15[c]	Subsequent Cycles D1[d]	End of Tx[e]	30-day post drug[f]	Long Term Follow Up[g]
Informed Consent[h]	X						
Background Information	X						
Inclusion/Exclusion Criteria[i]	X						
Serum Pregnancy Test[j]	X	X		X			
Vital Signs[k]	X	X	X	X	X		
Neuro & Physical Exam	X	X	X	X	X		
KPS[l]	X	X	X	X	X	X	
Con-Med & Adverse Event Assessments[m]		----------X----------					
12-lead ECG	X[n]			X[n]			
Imaging – MRI[o]	X[p]	X[p]		X[o]	X		
Response Assessment[q]				X	X		
Hematology[r]	X	X	X	X	X		
Serum Chemistry[s]	X	X	X	X	X		
Coagulation (PT/INR, PT, PTT)	X						
Submission of Archival Tissue	X[t]						X[w]
Plasma PK Collection[u]		X		X			
Abemaciclib Administration[v]		Every 12 hours		Every 12 hours			
Follow-Up Info							X

a. To be performed within 14 days of registration unless specified otherwise.

b. To be performed within 3 days prior to drug day 1 unless specified otherwise.

c. Cycle 1, Day 15 visit has a +/- 2 days window.

d. Within 3 days prior to day 1 drug, except imaging which is within 7 days prior to day 1 drug. Results of all assessments (aside from correlative studies) must be reviewed prior to taking drug for respective cycle.

e. End of treatment assessments to be performed within +/- 7 days of last study drug or within +/- 7 days of decision to end treatment. All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment or starting within 30 days of last study drug.

f. A contact/visit for review of concomitant medications, adverse events, and KPS (no neurologic exam required at 30-day FU time point) is to be performed at 30 days +7 days after the last study drug is given. This may be performed via documented phone conversation with a study nurse or clinician. All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment or starting within 30 days of last study drug.

g. Participants will be followed via medical record review until death for post-treatment therapies, progression information, and survival. Updates to the CRFs are to be made roughly every three months (+/- 1 month). Each site will be responsible for collecting information on their participants regarding all post-treatment therapies, start and stop dates of those therapies, the reason for stopping those therapies, and the date of death.

h. Per DF/HCC multi-center policy, must be obtained by MD attending. Informed Consent may be performed up to 28 days prior to registration.

i. Please see section 3. Genomic profiling data from previously performed sequencing and/or copy number array data to verify status of CDKN2A/B/C and RB1 must be available prior to registration.

j. Serum pregnancy test only for women of child bearing potential (as defined in Section 3.1.20). Serum pregnancy test within 7 days prior to Day 1 drug for registration purposes and repeated within 72 hours prior to Day 1 drug if original screening pregnancy test is not within 72 hours of Day 1 drug.

k. Vital signs: Weight, heart rate, blood pressure, respiration rate, temp. Height required only at baseline (any height within 1 year of registration is acceptable).

l. Karnofsky Performance Status (KPS)

m. Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator. Concomitant medications and reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.

n. EKG at screening and C2D1 only.

o. Imaging: gadolinium-enhanced contrast and non-contrast MRI. CT alternative, if MRI contraindicated. When feasible at a site, appendix G MRI Acquisition Protocol should be adhered to and the same imaging technique should be used in a participant throughout the trial. Imaging to be done at all odd cycles (C3D1, C5D1, etc.).

p. Within 14 days prior to registration (screening baseline scan). For the scan prior to treatment cycle 1 day 1, if steroids are added or increased between the date of the scan and the start of treatment, new baseline imaging is required.

q. Response assessment using RANO criteria, at time of imaging and as indicated clinically.

r. Hematology – erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

s. Biochemistry - albumin, alkaline phosphatase (ALP), bicarbonate (HCO_3), BUN, calcium, chloride, creatinine, glucose, magnesium, phosphorous, potassium, SGOT (AST), SGPT (ALT), sodium, total protein, total bilirubin, amylase and lipase, LDH and uric acid. If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed.

t. Archival tumor tissue per eligibility point 3.1.11 must be submitted to the DFCI Coordinating Center within 60 days of registration Archival tumor tissue per eligibility point 3.1.11 must be submitted to the DFCI Coordinating Center within 60 days of registration.

u. Required at C1D1 (pre-dose), C2D1, C3D1 and C4D1 for Cohort 2 participants. If a participant comes off study treatment prior to C4D1 then an end of treatment PK sample should be drawn. See section 9 for details on PK timing and processing requirements.

v. Please see protocol section 8.1.8 for abemaciclib administration instructions.

w. Tissue from subsequent surgery or post-mortem exam: In the event that the participant undergoes any subsequent surgery for tumor resection, if possible, tumor tissue will be acquired to evaluate potential mechanisms of resistance to therapy with abemaciclib. Dr. Keith Ligon should be consulted for specifications prior to surgery when possible.

11. MEASUREMENT OF EFFECT

This trial will utilize the criteria recently proposed by the Response Assessment in Neuro-Oncology (RANO) working group (Wen et al., 2010).

Radiologic assessment will be determined by the Response Assessment in Neuro-Oncology Working Group (RANO) Criteria using bidirectional tumor measurements with some modifications. In addition to imaging characteristics, these criteria include consideration of neurological function and corticosteroid use (Wen et al., 2010). The RANO Criteria is outlined in detail in this section.

Magnetic resonance imaging (MRI) is the most readily available and reproducible method of disease assessment and is required for this study. The largest and most representative lesions should be measured either on axial, coronal or sagittal slices, and chosen to be followed for response evaluation.

The recommended sequences are outlined in detail in Appendix G and should conform as closely as possible to the consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials.

11.1 Antitumor Effect – Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline (cycle 1, day 1 scan) and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

Measurable disease. Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Non-measurable evaluable disease. Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1cm.

11.2 Response/Progression Categories

Complete response (CR). All of the following criteria must be met:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No new lesions.
c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d) Participants must be on no steroids or on physiologic replacement doses only.
e) Stable or improved non-enhancing (T2/FLAIR) lesions
f) Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related

Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial response (PR). All of the following criteria must be met:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No progression of non-measurable disease.
c) No new lesions.
d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e) The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g) Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Progressive disease (PD). The following criterion must be met:

a) > 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids

and/or one or more of the of the following:

b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

c) Any new lesion
d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
e) Failure to return for evaluation due to death or deteriorating condition

Stable disease (SD). All of the following criteria must be met:
a) Does not qualify for CR, PR, or progression.
b) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
d) Stable clinically.

Unknown response status. Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

These RANO Response Criteria are also summarized in the following table:

Table 10.2: Summary of the RANO Response Criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease-<25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease
#: Progression occurs when any of the criteria with * is present
NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days from the date of registration.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

11.4 Evaluation of Best Response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Participants without measurable disease may only achieve SD or PD as their best "response."

11.5 Other Effect Measures

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

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

Performance Status:

Participants will be graded according to KPS score

Overall survival time:

From date of first dose (date of first post surgery treatment for participants in Cohort 1) to date of death due to any cause.

Progression-free survival time:

From date of first dose (date of first post surgery treatment for participants in Cohort 1) to date of progression or death. Participants who stop treatment for causes other than progression may be censored if other therapy is initiated or if regular assessments for assessing progression are no longer available.

11.6 Response Review at DFCI Coordinating Center

Central review of MRI or CT scans is planned for participants who achieve CR, PR, or PFS6.

Central review will be performed by Dr. Lee or her designee for registered subjects who have been determined by the enrolling institution as having achieved PFS6, complete radiographic response, or partial radiographic response. When a participant's films are requested by the DFCI Coordinating Center and Overall PI, all films of all views from pre-registration and subsequent scans must be submitted for central review. Once the Central Review is complete, the central review results can be made available to the local PI.

When imaging studies are requested by the Coordinating Center:

- All films of all views from pre-registration and subsequent scans must be submitted for central review.
- Transfer images to compact disc, labeled with study/case number and de-identified per institution's local policy.
- A copy of all scan reports must be attached for inclusion in the submission.
- A memo detailing what is being submitted should be included with submission (a template memo will be provided by the DFCI Coordinating Center)
- Ship to:

  Eudocia Quant Lee, MD c/o Kristen Fisher
  Center for Neuro-Oncology
  Dana-Farber Cancer Institute
  450 Brookline Avenue, LG1B12A
  Boston, MA 02215
  Telephone: 617-632-4341

The submitting institution is responsible for the costs of shipping and handling.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with ODQ
On Study Form	Within 30 days of registration
Baseline Assessment Form	Within 30 days of registration
Treatment Form	Within 14 days of treatment administration
Adverse Event Report Form	Within 14 days of AE assessment/notification
Response Assessment Form	Within 14 days of the response assessment
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Data Safety Monitoring

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

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30

days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This will be an open label Phase II trial in participants with recurrent GBM. Cohort 1 and Cohort 2 will enroll concurrently. In Cohort 1, to ensure that adequate abemaciclib penetrates into the tumors and inhibits cellular proliferation, 15 participants with recurrent GBM who require reoperation will be treated with abemaciclib prior to surgery. After recovery from surgery, participants will receive abemaciclib until disease progression or the development of unacceptable toxicities. In Cohort 2, participants will receive abemaciclib without undergoing prior surgery. The two cohorts will be analyzed separately.

In Cohort 1 we will attempt to characterize the pharmacokinetic (PK) uptake of abemaciclib in brain. A single-time point brain-to-plasma ratio will be calculated for each participant with a paired plasma and brain sample, followed by a descriptive statistical analysis (mean, SD, CV% or median (range)). In addition, both a naive pool strategy of all brain samples as well as a non-linear mixed effect approach will be explored in an attempt to provide a better estimate of time-course of brain uptake, the total brain exposure over a dosing interval (AUC0-24) and the brain-plasma tissue partitioning coefficient (Kpt).

Cohort 1 will also assess for pharmacodynamic (PD) evidence of target inhibition in brain tissue. We will evaluate tumor tissue after treatment with abemaciclib for reduced RB1 signaling,

cellular proliferation, and increased cell death by immunohistochemistry for pRB1, Ki67, and cleaved caspase 3. The IHC effects will be evaluated by pathologist manual scoring of each marker as well as morphometric techniques to determine change relative to pre-abemaciclib biopsy which will also be stained. These results will be compared to a group of 15 patient samples who received treatment only with standard of care TMZ and RT. Results of the two cohorts will be compared statistically to determine whether significant changes are noted.

The primary goal of Cohort 2 is to determine the therapeutic efficacy of abemaciclib as measured by PFS6. Treatment duration will be measured in 4-week cycles. Participants will remain on treatment until tumor progression, as long as there are no unacceptable toxicities. Responses will be assessed by clinical examinations every 4 weeks and MRI scans every 8 weeks.

13.2 Endpoints

13.2.1 Cohort 1

13.2.1.1 Primary endpoint

- Abemaciclib levels in tumor tissue
- Pharmacokinetics

13.2.1.2 Secondary endpoints

- Effects on tumor cell proliferation and tumor cell death
- Safety

13.2.1.3 Exploratory endpoints

- Effects of abemaciclib on primary GBM cell lines

13.2.2 Cohort 2

13.2.2.1 Primary endpoint

- PFS6

13.2.2.2 Secondary endpoints

- Radiographic response rate
- Median progression free survival
- Overall survival
- Pharmacokinetics
- Safety

13.2.3 Exploratory endpoints

- Correlate benefit from abemaciclib treatment with molecular phenotype/genotype of tumor
- Investigate mechanisms of resistance to abemaciclib by examining tumor tissue obtained from patients who progress on treatment, when available, with pretreatment tumor.

13.3 Sample Size/Accrual Rate

A sample size of 15 participants is planned for the surgical sub-study (Cohort 1), with an accrual rate of 2-3 participants per month. This results in an anticipated enrollment period of 5-8 months

for Cohort 1.

Thirty-two participants will be accrued to Cohort 2 and will occur concurrently with Cohort 1. With an accrual rate of 4-5 participants per month, the anticipated enrollment period will be 7-9 months for Cohort 2.

The primary endpoint for Cohort 2 will be the proportion of participants who are progression free at 6 months (PFS6). Historical comparison data suggest that ineffective therapies in recurrent GBM have a PFS6 rate of approximately 9-16% (Lamborn et al., 2008; Wong et al., 1999). The sample size was chosen to discriminate between 15% and 35% PFS6 rates for the GBM patients. With accrual of 32 GBM patients, the trial would be considered successful if 8 achieved PFS6. This yields 0.92 power to detect a 35% PFS6 rate, with a 0.90 probability of rejecting the treatment regimen if the PFS6 rate is only 15%.

Since the primary endpoint is PFS6, analyses will be not performed until the 6 month PFS status of all participants is determined (or the participant has been permanently censored for PFS for reasons such as loss-to-follow-up or initiation of alternative therapies).

For the primary endpoint of PFS6, participants without documentation that they are progression free at 6 months – no progression at the 24 week scan – will be considered failures. Additional information about PFS will be provided using Kaplan Meier curves. For those analyses participants will be censored for PFS at the date of the last scheduled scan if they initiate alternative therapy or cease to have regularly scheduled follow up scans.

13.4 Analysis of Secondary and Exploratory Endpoints

Response rate will be the proportion of participants with measurable disease who experience complete or partial radiographic response determined by the RANO Criteria (Wen et al., 2010). Progression free survival, PFS6, and overall survival will be calculated using standard statistical methods. Safety will be summarized using descriptive statistics. Participants in Cohort 2 will not be replaced for any reason. If a subject enrolled in Cohort 1 is found at the time of on-treatment re-resection to have only necrosis and not recurrent disease, then s/he may remain on treatment but should be replaced for evaluation of endpoints.

In Cohort 1 & 2 plasma, and Cohort 1 tumor tissue levels of abemaciclib will be determined by liquid chromatography coupled with tandem mass spectrometry. Descriptive details of steady-state trough plasma levels, CSF and tumor tissue concentrations and tumor tissue to plasma ratios will be provided.

Other pharmacodynamic studies including immunohistochemistry and quantitative IHC analysis will be performed as in Section 9.0. Effects of abemaciclib on tumor cell proliferation and tumor cell death will be measured using immunohistochemistry for pRB1, Ki-67 and Cleaved Caspase 3. In general the pharmacodynamic and neuro-imaging results will be summarized in a descriptive manner with comparison between pre- and post-treatment assay results when possible.

Beyond the assessment of "success", more detailed analyses of the biological correlate data are exploratory. The statistical analysis will depend on the amount and quality of the data obtained as well as the overall success of the treatment.

13.5 Reporting and Exclusions

Evaluation of toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.
Evaluation of response. Only those participants who have measurable disease present at baseline and have received at least one dose of therapy will be considered evaluable for response.
Evaluation of other efficacy endpoints. All participants who receive at least one dose of study treatment (post surgery for those in Cohort 1) will be included in analyses of all other endpoints. Time-to-event endpoints will be measured from first dose date (first post-surgery dose date for those in Cohort 1).

14. DISCIPLINE REVIEW

14.1 Central Pathology Review

At screening archival tumor tissue (as described in section 3.1.10) from the pre-registration surgery must be submitted for review along with accompanying pathology, surgical, and genomic profiling reports. The purpose of this review is to verify the histologic diagnosis, loss of CDKN2A/B, and intact RB.

Section 9.2 contains details regarding shipping and handling.

If the participant's slides have been reviewed on a previous IVY study and there has been no interim surgery or biopsy the slides do not need to be re-submitted. The site must submit a copy of the previous submission forms with the review results to the IVY central office as documentation for the new study.

Central pathology and molecular review will be performed at DFCI by Dr. Keith L. Ligon, MD, PhD or designee. Materials for pathologic study will be stored in the lab of Dr. Ligon following participant registration in the trial.

The submitting institution is responsible for the costs of shipping and handling.

14.2 Central Radiology Review

Please see section 11.6 for details.

15. PUBLICATION PLAN AND DISCLOSURE POLICY

Participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted herein is prohibited. Data generated by this study must be available

for inspection upon request by representatives of the FDA, national and local health authorities, Pharmaceutical company providing the agent, and the IRB for each study site, if appropriate. The intention is to publish the results of this study in a medical journal such as Journal of Clinical Oncology or Neuro-Oncology. Results may be presented at national meetings of the American Society for Clinical Oncology and/or Society for Neuro-Oncology. Results will be made publicly available as required by law.

Clinical Trial Data Bank

The DF/HCC Principal Investigator (Dr. Eudocia Quant Lee) or designee will register this clinical trial at www.clinicaltrials.gov, the US National Library of Medicine website prior to initiation of the study. This website provides regularly updated information about US government and privately supported clinical research in human volunteers. In addition, the DF/HCC Principal Investigator or designee will make the results of this study publicly accessible by publication and by posting the results on www.clinicaltrials.gov

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APPENDIX A PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX B MULTI-CENTER DSMP

DFCI IRB Protocol #: **16-383**

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: Among the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CHB, BWH), the Dana-Farber Cancer Institute will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (FDA, etc.). The Lead Institution is the home of the Overall PI.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. For this protocol the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator.

Participating Institution: An institution that desires to collaborate with DF/HCC and commits to accruing participants to the DF/HCC protocol. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety

monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Eudocia Quant Lee, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC ODQ.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violations submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal Wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation of all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.

- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating

Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB
- Participating Institution’s IRB approval for all amendments
- Annual approval letters by the Participating Institution’s IRB

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any

information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ case number (as described below). Participant initials may be included or retained for cross verification of identification

3.7 DF/HCC Multi-Center Protocol Registration Policy

Eligible participants will be registered onto trial with the DF/HCC Office of Data Quality (ODQ) central registration system (by a Coordinating Center specialist, if participant is at a non-DF/HCC site). Registration with ODQ must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A qualified member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the ODQ Registrar (a Coordinating Center specialist, if participant is at a non-DF/HCC site) of participant status changes as soon as possible.

In order to register a participant onto study, the following must be done:

- Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
- Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for**

registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

3.7.1 Participant Registration at a non-DF/HCC Site

To register a participant at any non-DF/HCC site, the subsequent procedure is to be followed:

1. The participating site's data manager/coordinator/research nurse should contact the lead-site Designee (Multi-Center Coordinating Center specialist) via telephone or email to:

- Notify regarding the pending registration
- Confirm the methods of sending documents and communication for registration
- Communicate desired timeline of the registration (i.e. within the hour, the next day) via e-mail to NeuroOnc_Coor@dfci.harvard.edu

2. The data manager/coordinator/research nurse should then send the following documents to the Coordinating Center specialist:
    - Completed DF/HCC study specific Eligibility Checklist
    - Copy of protocol required test results (e.g. coagulation studies, hematology panel, serum pregnancy test, serum chemistry panel, urinalysis -- all as applicable per protocol)
    - Copy of the pathology and surgical reports
    - List of current concomitant medications (obtained within the protocol-specified screening window) including sign/date by RN/other clinician and documentation of when reviewed/confirmed with patient
    - Copy of signed informed consent form
    - Copy of signed HIPAA authorization form (if separate from the informed consent document)
    - Copy of clinic note(s) and other medical records that document consenting process, screening and eligibility, if available***

Documents will be transmitted via one of the following methods:
- *Scanned and emailed to:* NeuroOnc_Coor@dfci.harvard.edu
- *Faxed to: 617-394-2683*

*** *The Coordinating Center Specialists would like to review and monitor participant*

eligibility, informed consent, screening and baseline assessments on all participants. Providing a complete set of source documents prior to registration may delay registration. Participating Institutions will work with the Coordinating Center Specialists to determine what documents may feasibly be available for review prior to enrollment, and these documents are to be provided for pre-enrollment review. A complete set of documents will be provided to the Coordinating Center after registration; the timeline will be determined by the Coordinating Center Specialist based on the study team's experience with the trial and prior monitoring findings. If there are persistent issues with eligibility at a site or with a study overall, the Coordinating Center may require that all source documentation relevant to participant eligibility be provided prior to proceeding with participant registration.

2. After having received all transferred documentation, the Designee (Coordinating Center specialist) will review the documents to verify eligibility, and notify the participating site of the result.
3. The Coordinating Center Designee will register the participant with ODQ Registrar, and subsequently inform the participating site of the successful registration via Fax or email, to include:
    - Participant case number
    - Applicable Dose Treatment level and treatment arm assignment
4. The Coordinating Center Designee will follow-up to confirm registration.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each participating institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the Overall PI and DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

Protocol violations occurring at a Participating Institution will be submitted to that site's own IRB per the IRB's reporting policy. Whether or not a violation needs to be reported to the local IRB, notification to the Coordinating Center of any violation should occur in a timely manner. If a report is made to the Participating Institution's IRB, the report and determination should also be forwarded to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center and IRB, both DFCI and local as applicable.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Advert Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Intuitions will review and submit to their IRB according to their institutional policies and procedures.

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their intuitional policies and procedures.

3.11 Data Management

The DF/HCC CTRIO develops case report forms (eCRFs), for use with the protocol. These forms are designed to collect data for the study. The DF/HCC CTRIO provides a web based training for eCRF users.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned within the electronic data capture (eDC) system.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis. Required timelines for data submission based on form type are defined in protocol section 12.1.2.

4.0 REQUISITIONING INVESTIGATIONAL DRUG

Participating Institutions will order their own investigational agent (Abemaciclib) directly from Lilly using the Drug Supply Request Form. Please allow for 3-5 business days for drug to arrive after the order is submitted. Additional information for ordering Abemaciclib can be found in Section 8.1.9 of the protocol body. The Participating Institution will ensure that the pharmacy will be able to receive and store the agent according to state and federal guidelines. The local IRB should be kept informed of who will supply the agent (i.e., Lilly) so that any regulatory responsibilities can be met in a timely fashion.

5.0 MONITORING: QUALITY CONTROL

Monitoring and oversight of a clinical trial are federally mandated for all IND held trials. This quality control process for a clinical trial requires verification of protocol compliance and data accuracy and the protection of the rights and welfare of participants. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institutions may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Remote monitoring of participant eligibility, human subject's protection via the initial informed consent process, and screening evaluation completion will occur via a two stage process.

- Prior to registering each participant, a Coordinating Center Specialist will review the source documentation provided in the enrollment packet (see Section B 3.7.1) to confirm, (a) that based on all objective measurements (lab tests; pathology report) that the prospective participant is eligible, (b) that the objective measurements were performed per protocol within the appropriate protocol-defined windows, (c) that the prospective participant does not have concomitant medication that precludes eligibility, and, if documentation is provided, (d) that the consenting process was adequate/adequately documented, (e) that the participant met criteria for eligibility. Furthermore, using the Eligibility Screening Worksheet, the Specialist will verify that the investigator has indicated that he/she has reviewed and confirmed as "eligible" the prospective participant
- The Specialist will review the second set of participant-specific source documents provided by study teams (see Section B 3.7.1) to confirm that (a) all screening and baseline assessments were completed per protocol, including AE assessment, and documented appropriately, (b) that all eligibility criteria were met and appropriately documented, and, if not previously reviewed, (c) that the consenting process was adequate/adequately documented. The timeline for this review will be based on the experience with the study team, and the study team's experience with the protocol.

Interim monitoring visits will occur on the following schedule:

- Once a site has registered a participant, up until all participants (and planned participants) have discontinued taking study agent (may be in follow-up), interim monitoring visits will occur at least twice per year, alternating between on-site visits and virtual monitoring visits. The first on-site interim monitoring visit will occur approximately two months after the registration of the site's first participant.
- Once a site is closed to accrual and all participants have discontinued study agent, interim monitoring visits will occur virtually, and on-site as needed, at least annually until study completion.

On-site and remote monitoring visits may include but are not limited to the following:

- Adverse events and altered results
- Response assessment including measurements and clinical assessments

- Study drug administration and accountability, to include a visit to the pharmacy
- Concomitant medications
- Re-consenting
- Presence of key documents: original consent, eligibility and screening source information, registration confirmation, off-treatment form, off-study form, transfer of samples
- Reason off treatment and reason off study
- Regulatory binder: accessibility, organization, random sampling for relevant documents and correspondence with the trial master file.
- Visit with the site's principal investigator:
    - Review of site's accrual rate and, when possible, sign-off on the screening/enrollment log to date
    - Review of deviations and violations, and, when possible, sign-off on the deviation/violation log
    - General study progress
- Timeliness of data completion (at the time of the INTERIM MONITORING VISIT and history since last report)
- Attendance at teleconferences since last report
- Completion of study procedures per protocol (procedures complete and within windows)
- Agreement between recorded results and the AE log.
- Analysis of data for any events that met criteria for Reportable Adverse Events, dose holds, dose reductions, or discontinuation of treatment.
- Review the eDC for any Reportable Adverse Events, holds, dose reductions, and discontinuation of treatment to ensure the justification and follow-up are sufficiently documented in the eDC.
- Agreement between drug accountability records and drug administration
- Agreement and completion of the trial master file

Timely transfer of copies of regulatory documents including pharmacy records. The Coordinating Center is mandated to maintain a Trial Master File, which is a copy of the site's regulatory binder.

- Regulatory documents should be sent electronically to the Coordinating Center in lieu of being collected at the time of the monitoring visit; they should be sent upon receipt/creation to the Coordinating Center, and not wait until time of request.
- Original forms (i.e. 1572s, protocol receipts etc.) should be maintained with the site's regulatory binder until requested by the Coordinating Center. When possible, the Coordinating Center will provide a stamped certified copy of the original for the site's regulatory binder.
- Special consideration should be placed on the timely transfer of pharmacy regulatory binder documents, since the Coordinating Center is responsible for tracking all study

agent. Copies of DARs and shipping receipts should be provided to the Coordinating Center via electronic submission on request. The Coordinating Center is to be copied on all drug requests.

Regular all-sites teleconferences to occur at least monthly, bi-weekly when needed. During the teleconferences, sites will be expected to convey the following information:

- Updates on participants taking agent: holds, dose reductions, significant events, how participant is doing, whether or not underwent re-consenting
- Protocol status – which version is being used, and the status of any amendments
- Any Reportable Adverse Events or Deviations/violations that have yet to be communicated to the sponsor team (informing the sponsor should not wait for the call, and the call does not supplant communicating the events via the regular email methods of communication).
- Review of prospective participants

If sites are not able to have a representative participant, they should email this information. During the teleconferences, the Coordinating Center Specialist will provide the following information at least monthly:

- Accrual/enrollment updates
- Pending amendments
- Safety reports circulated or to be circulated
- ODQ-generated numbers and percentage of missing of missing forms, number of open queries with date of oldest open query, and, for participants on treatment, the date of their last study agent form
- To be updated at least every three months: for participants in follow up, the date of their last follow-up.
- Updates (newly discovered events) of deviations, violations
- Updates of Reportable Adverse Events

Monthly circulation of Central Logs and Missing Forms Reports. Approximately monthly, and usually at the time of the teleconferences, the Coordinating Center Specialist will circulate the updates to the Central Screening Enrollment Log, Central Deviation/violation log, Central Reportable Adverse Event Log, and ODQ generated Missing Forms Reports.

Initial training. To aid with protocol compliance, the Coordinating Center will provide a teleconference site initiation visit (approximately 3 hours) and operations manual (as needed) prior to activation of the study at each site. In addition, the Coordinating Center will provide an overview of the eCRFs with appropriate study team members, after each site has registered their first participant.

The Coordinating Center will be available to all sites' study team members for resolving questions concerns and facilitating compliance.

Because of limited on-site monitoring visits, participating sites will be required to submit (either electronically or via paper) requested source documents to the Coordinating Center

for source verification.

5.2 Evaluation of Participating Institution Performance

5.2.1 Monitoring Reports

The DF/HCC Sponsor will be provided with all monitoring reports for on-site and remote monitoring of Participating Institutions for review to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

As this is a Phase II study, Participating Institutions accrual requirement of 3 participants per site annually will be implemented.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and

corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX C REPORTABLE AE COVERSHEET

DF/HCC Protocol No. 16-383 Eli Lilly Protocol No. I3Y-MC-009

Date:_____ Number of pages including cover sheet:_____

Please check off recipient of this AE:

☐ Eudocia Quant Lee, MD (Overall PI) at Dana-Farber Cancer Institute Coordinating Center
Email: NeuroOnc_SAE@dfci.harvard.edu

☐ Eli Lilly and Company
MAILINDATA_GSMTINDY@LILLY.COM

From:	Institution:
Phone No.:	Fax No.:

Participant No. and Initials:
Date Event Met Reporting Criteria (as defined per protocol):
Type of Report: ☐Initial ☐Follow-up
Will this event be reported to your local IRB? ☐ Yes ☐ No

Event #1 Description:	Event #2 Description (if applicable): *NOTE: Please use additional sheet if > 2 events are being reported*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5
Historical/Known Correlation to **Abemaciclib**: ☐Expected ☐Unexpected *NOTE: Please refer to protocol section 6.1*	Historical/Known Correlation to **Abemaciclib**: ☐Expected ☐Unexpected *NOTE: Please refer to protocol section 6.1*
Attribution to **Abemaciclib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite	Attribution to **Abemaciclib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite
Reporting Investigator (please print):	

Signature of Reporting Investigator: _____ Date: _____

APPENDIX D INFORMATION ON POSSIBLE DRUG INTERACTIONS

Please see Section 5.4 for detailed instructions on concomitant medications, including use in clinically required situations. Please note that these lists may not be comprehensive.

Table D-1: List of CYP3A Inhibitors and CYP3A Inducers

CYP3A4,5,7 inhibitors	CYP3A4,5,7 inducers
indinavir[1]	carbamazepine
nelfinavir[1]	efavirenz
ritonavir[1]	nevirapine
clarithromycin[1]	phenobarbital
itraconazole[1]	phenytoin
ketoconazole[1]	pioglitazone
nefazodone[1]	rifabutin
erythromycin[2]	rifampin
grapefruit juice[2]	St. John's Wort
verapamil[2]	troglitazone
suboxone[2]	
diltiazem[2]	
cimetidine[3]	
amiodarone	
NOT azithromycin	
flyvoxamine	
troleandomycin	
voriconazole	

1. A Strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance. Strong inhibitors are **prohibited** per protocol section 5.4.
2. A Moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
3. A Weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

This list of CYP3A inhibitors and inducers was compiled from the Indiana University School of Medicine's *P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table.* For the most comprehensive and up-to-date list, please go to **http://medicine.iupui.edu/clinpharm/ddis/** .

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed October 2015

Table D-2: List of CYP450 Substrates to be used with caution

CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2D6	CYP3A4,5,7
clozapine	artemisinin	paclitaxel	NSAIDs:	Beta Blockers:	Macrolide antibiotics:
cyclobenzaprine	bupropion	torsemide	diclofenac	carvedilol	clarithromycin
duloxetine	cyclophosphamide	amodiaquine	ibuprofen	S-metoprolol	erythromycin
fluvoxamine	efavirenz	cerivastatin	naproxen	propafenone	NOT azithromycin
haloperidol	liosfamide	repaglinide	piroxicam	timolol	telithromycin
imipramine	ketamine		Oral Hypoglycemics:	Antidepressants:	Anti-arrhythmics:
mexiletine	meperidine		tolbutamide	amitriptyline	quinidine→3-OH
nabumetone	methadone		glipizide	clomipramine	Benzodiazepines:
naproxen	nevirapine		glyburide	desipramine	alprazolam
olanzapine	propofol		Angiotensin II Blockers:	duloxetine	diazepam→3-OH
riluzole	selegiline		iosartan	fluoxetine	midazolam
tacrine			irbesartan	imipramine	triazolam
theophylline			Others:	paroxetine	Immune Modulators:
tizanidine			celecoxib	Antipsychotics:	cyclosporine
triamterene			fluvastatin	haloperidol	tacrolimus
zileuton			phenytoin	risperidone	sirolimus
zolmitriptan			rosiglitazone	thioridazine	HIV Antivirals:
			torsemide	Others:	indinavir
			valproic acid	aripiprazole	ritonavir
			warfarin	atomoxetine	saquinavir
			zafirlukast	codeine	nevirapine
				dextromethorphan	Prokinetics:
				doxepine	cisapride
				flecainide	Antihistamines:
				mexiletine	astemizole
				ondansetron	chlorpheniramine
				oxycodone	Calcium Channel Blockers:
				risperidone	amlodipine
				tamoxifen	diltiazem
				tramadol	felodipine
				venlafaxine	nisoldipine
					nitrendipine
					verapamil
					HMG CoA Reductase Inhibitors:
					atorvastatin
					lovastatin
					NOT pravastatin

					NOT rosuvastatin
					simvastatin
					PDE-5 Inhibitors:
					sildenafil
					tadalafil
					vardenafil
					Others:
					alfentanyl
					aripiprazole
					Boceprevir
					busprione
					carbamazepine
					gleevec
					haloperidol
					pimozide
					quinine
					tamoxifen
					telaprevir
					trazodone
					vincristine

This list of CYP substrates was compiled from the Indiana University School of Medicine's *P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table.* For the most comprehensive and up-to-date list, please go to **http://medicine.iupui.edu/clinpharm/ddis/** .

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed October 2015

APPENDIX E ABEMACICLIB DOSING INSTRUCTIONS & DRUG DIARY (Post-Surgery Cohort 1 & Cohort 2)

To be completed by study personnel:

Patient ID #_____ Patient Initials: _____ Cycle #: _____ Month & Year: _____ Abemaciclib Dose: _____mg, two times a day.

TAKE ____ pill(s) in the morning and ____ pill(s) in the evening.

Abemaciclib Description:

- Your study drug (Abemaciclib) is supplied as 50 mg mixture beige tablet.

Abemaciclib Instructions – When and How:

- Take study drug (Abemaciclib) twice a day, once in the morning and once in the evening.
- Take the drugs at approximately the same time each morning and evening, so that you are taking the drugs 12 hours apart. At the start of cycles 2, 3 and 4 you will be asked to take your morning abemaciclib after your clinic visit.
- Take the pill(s) with a glass of water and swallow them whole; do not chew them or crush them. Abemaciclib can be taken with or without food.
- Do not skip any doses.
- If you forget to take your pills in the morning you can take your missed dose up to 6 hours after your normally scheduled time. If it has been more than 6 hours, skip the dose and take the next scheduled dose at the usual time in the evening (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you forget to take your pills in the evening, you can take your missed dose up to 6 hours after your normally scheduled time. If it has been more than 6 hours from the missed dose (i.e., less than 6 hours to your next scheduled dose), skip the dose and take the next scheduled dose at the next usual time (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you vomit your pills, write this down in your pill diary. Do not take a replacement dose. Take the next scheduled dose as usual (one dose only). Please call your study nurse or doctor to discuss vomited doses.

Additional Instructions:

- You must avoid eating or drinking any foods with Seville oranges (like marmalade), grapefruit or foods or drink with grapefruit, and any exotic fruits during the entire treatment period.
- You should drink 8 to 10 glasses of clear liquids a day for the entire treatment period.
- Keep your study drug in the original container(s) at room temperature. Keep study drug away from children, persons cannot read the label, and pets.
- Do not throw away empty bottles, and do not throw the study drug in the trash or flush into the toilet.
- Bring this diary, all pill bottles, and any unused pills to each clinic visit. Your Treatment Team will collect your diary, all pill bottles and any unused study drug, and you will be given a new pill diary at that time.
- Contact your study doctor or nurse if you are having any new or worsening side effects. Contact your study doctor or nurse as soon as possible if you are experiencing diarrhea.
- Do not begin any new medication, over-the-counter drug, or herbal preparation without first checking with your study doctor or nurse to determine if it is acceptable to take while on this study.
- Each cycle is 28 days of morning and evening pills. If you start the cycle in the evening (P.M. dose), you may end the cycle in the morning of the 29th day.

Each cycle is 28 days of morning and evening pills. If you start the cycle in the evening (P.M. dose), you may end the cycle in the morning of the 29th day.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials
Day 8	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials
Day 15	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A. M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ____________ P.M. DOSE No. of pills: ________ Time: ____________ __________ Initials

Each cycle is 28 days of morning and evening pills. If you start the cycle in the evening (P.M. dose), you may end the cycle in the morning of the 29th day.

Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials
Day 29						
Date: A.M. DOSE No. of pills: ________ Time: ______________ P.M. DOSE No. of pills: ________ Time: ______________ __________ Initials						

Participant/Guardian Signature: ________________________________ Date: ________________

To be completed by study personnel: # of 50 mg Bottles Returned: ________ # of 50 mg Pills Returned: ________

Compare with drug diary entries made by participant or guardian. If discrepancy (in the # of bottles or the # of pills returned), please reconcile:

Study Personnel Signature: ______________________________ Date: ________________

APPENDIX F ABEMACICLIB DOSING INSTRUCTIONS & DRUG DIARY (Cohort 1 Pre-Surgery)

To be completed by study personnel:

Patient ID #_____ Patient Initials: _____ Pre-Surgery Cycle Month & Year: _____ Abemaciclib Dose: _____mg, two times a day.

TAKE ____ pill(s) in the morning and ____ pill(s) in the evening.

Abemaciclib Description:

- Your study drug (Abemaciclib) is supplied as 50 mg mixture beige tablet.

Abemaciclib Instructions – When and How:

- Take study drug (Abemaciclib) twice a day, once in the morning and once in the evening.
- Take the drugs at approximately the same time each morning and evening, so that you are taking the drugs 12 hours apart. Morning and evening doses should be taken as close to a 7AM & 7PM schedule as possible (7 in the morning, 7 at night, 7 the next morning, and so on).
- Take the pill(s) with a glass of water and swallow them whole; do not chew them or crush them. Abemaciclib can be taken with or without food.
- Do not skip any doses.
- If you forget to take your pills in the morning you can take your missed dose up to 6 hours after your normally scheduled time. If it has been more than 6 hours, skip the dose and take the next scheduled dose at the usual time in the evening (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you forget to take your pills in the evening, you can take your missed dose up to 6 hours after your normally scheduled time. If it has been more than 6 hours from the missed dose (i.e., less than 6 hours to your next scheduled dose), skip the dose and take the next scheduled dose at the next usual time (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you vomit your pills, write this down in your pill diary. Do not take a replacement dose. Take the next scheduled dose as usual (one dose only). Please call your study nurse or doctor to discuss vomited doses.
- **On the day of surgery**, you will be asked to take your morning dose at the hospital; therefore, please bring your pills with you. Do not take any further doses after surgery. Return any remaining pills to the study team.

Additional Instructions:

- You must avoid eating or drinking any foods with Seville oranges (like marmalade), grapefruit or foods or drink with grapefruit, and any exotic fruits during the entire treatment period.
- You should drink 8 to 10 glasses of clear liquids a day for the entire treatment period.
- Keep your study drug in the original container(s) at room temperature. Keep study drug away from children, persons cannot read the label, and pets.
- Do not throw away empty bottles, and do not throw the study drug in the trash or flush into the toilet.
- Bring this diary, all pill bottles, and any unused pills to each clinic visit. Your Treatment Team will collect your diary, all pill bottles and any unused study drug, and you will be given a new pill diary at that time.
- Contact your study doctor or nurse if you are having any new or worsening side effects. Contact your study doctor or nurse as soon as possible if you are experiencing diarrhea.
- Do not begin any new medication, over-the-counter drug, or herbal preparation without first checking with your study doctor or nurse to determine if it is acceptable to take while on this study.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date: A.M. DOSE No. of pills: _______ Time: ______________ P.M. DOSE No. of pills: _________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: _______ Time: ____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: _______ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials
Day 8	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date: A.M. DOSE No. of pills: _________ Time: ______________ P.M. DOSE No. of pills: _________ Time: ______________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M.DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: _____________ P.M. DOSE No. of pills: ________ Time: _____________ __________ Initials

Please stop taking abemaciclib after on-study surgery until you are evaluated by the study team. All unused study medication should be returned to the study team.

Participant/Guardian Signature: ________________________________ Date: _______________

To be completed by study personnel: # of 50 mg Bottles Returned: ________ # of 50 mg Pills Returned: ________

Compare with drug diary entries made by participant or guardian. If discrepancy (in the # of bottles or the # of pills returned), please reconcile:

Study Personnel Signature: _____________________________ Date: _______________

APPENDIX G MRI ACQUISITION PROTOCOL

Brain MRI will be acquired at baseline and every 8 weeks after treatment initiation as detailed in Section 10 Study Calendar. All MRI exams will be performed based on standardized parameters recommended by the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee (Ellingson et al. Neuro Oncol. 2015 Sep;17(9):1188-98). The following sequences are included: (i) parameter-matched precontrast and postcontrast inversion recovery-prepared, isotropic 3D T1-weighted gradient-recalled echo; (ii) axial 2D T2-weighted turbo spin-echo acquired after contrast injection and before postcontrast 3D T1-weighted images to control timing of images after contrast administration; (iii) precontrast, axial 2D T2-weighted fluid-attenuated inversion recovery; and (iv) precontrast, axial 2D, 3-directional diffusion-weighted images. The T2-weighted sequence should be performed following contrast injection, before acquisition of T1-weighted post-contrast sequences. The protocol can also include additional advanced imaging sequences such as perfusion weighted imaging (PWI) and susceptibility weighted imaging (SWI). Detailed parameters are listed in Table below.
When possible, MRI exams should be done using the same MRI scanner for each subject. If this is not achievable, patients should at the very least be scanned on MRI scanners with the same field strength (1.5T or 3T). The chemical composition and dose of gadolinium contrast agents should also be the same for each patient during trial and should be explicitly documented on the MR system during acquisition or labeled in the DICOM header.

Table: MRI Protocol

1. Localizer
2. Axial 3D T1w (IR-GRE)[1]
3. Ax 2D FLAIR[2]
4. Ax 2D SS-EPI DWI[3]
5. Ax GRE or Ax SWI
6. Contrast Injection
7. Ax EPI Perfusion
8. Ax 2D SE T2w[4]
9. Axial 2D SE T1w
10. Axial 3D T1w (IR-GRE)[1]

Sequence		TSEc	SS-EPIg	Contrast Injectiona	TSEc	IR-GREe,f
Plane	Axial	Axial	Axial	Sagittal/axial		
Mode	2D	2D	2D	3D		

1. TR [ms] 2100, TI [ms] 1100, Flip angle 10°–15°, Frequency ≥172, Phase ≥172, NEX ≥1, FOV 256 mm, Slice thickness ≤1.5 mm. Gap/spacing 0, Parallel imaging up to 2x
2. TR [ms] >6000, TE [ms], 100–140, TI [ms] 2000–2500, Flip angle 90°/≥160°, Frequency ≥256, Phase ≥256, NEX ≥1, FOV 240 mm, Slice thickness ≤4 mm, Gap/spacing 0, Parallel imaging up to 2x
3. TR [ms] >5000, TE [ms] , Flip angle 90°/180°, Frequency ≥128, Phase ≥128, NEX ≥1, FOV 240 mm, Slice thickness ≤4 mm, Gap/spacing 0, Parallel imaging up to 2x, b = 0, 500, 1000 s/mm2 ≥3 directions
4. TR [ms] >2500, TE [ms], 80–120, Flip angle 90°/≥160°, Frequency ≥256, Phase ≥256, NEX ≥1, FOV 240 mm, Slice thickness ≤4 mm, Gap/spacing 0, Parallel imaging up to 2x. Post-contrast sequence (10) should be obtained within 8 minutes from time of contrast injection.