A SINGLE-ARM, OPEN-LABEL, PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF ABEMACICLIB IN PATIENTS WITH RECURRENT OLIGODENDROGLIOMA

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List of Abbreviations

AE: Adverse event

AIDS: Acquired immunodeficiency syndrome

ALP: alkaline phosphatase

ALT: Alanine aminotransferase

ART: Antiretroviral therapy

AST: Aspartate aminotransferase

AUC: Area under the curve

BID: twice daily

C: Celsius

CBC: Complete blood count

CEST: Chemical Exchange Saturation Transfer

CIC: Capicua transcriptional repressor

CL: Plasma clearance

CL_{cr}: Creatinine clearance

CLIA: Clinical Laboratory Improvement Amendments

Cmax: mean peak observed concentration

CNS: Central Nervous System

CR: Complete response

CRF: Case report form

CTCAE: Common Terminology Criteria for Adverse Events

CV: Coefficient of variation

DLT: Dose-limiting toxicity

ECOG: Eastern Cooperative Oncology Group

eCRF: electronic case report form

EOT: end of treatment

FDA: Food and Drug Administration

FFPE: Formalin-fixed paraffin-embedded

FLAIR: fluid attenuation inversion recovery

GBM: Glioblastoma

GGT: gamma-glutamyl transferase

GI: Gastrointestinal

GLP: Good Laboratory Practice

Gy: Gray

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HCG: Human chorionic gonadotropin

hfRT: hypofractionated radiotherapy

Hgb: Hemoglobin

HIV: Human immunodeficiency virus

ICHL International Conference of Harmonisation

IDH: Isocitrate dehydrogenase

IHC: immunohistochemistry

IMRT: Intensity-modulated radiation therapy

INR: International normalized ratio

IRB: institutional review board

IU: International Units

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IUD: intrauterine device

IV: Intravenous (ly)

kDa: kilodaltons

Kg: Kilograms

L: liter

LDH: Lactate dehydrogenase

LFTs: liver function tests

Mg: Milligrams

MGMT: O6-Methylguanine-methyltransferase

mL: milliliter

mM: millimolar

MRI: Magnetic Resonance Imaging

MTD: maximal tolerated dose

NA: Not available

NOAEL: no-observed-adverse-effect-level

ORR: Objective response rate

OS: Overall survival

PAD: pharmacologically active dose

PCR: polymerase chain reaction

PD: Progressive disease

PFS: Progression-free survival

PFS-6mo: Progression-free survival rate at 6 months

P-gp: p-glycoprotein

PK: Pharmacokinetic (s)

PR: Partial response

PS: Performance status

PT: Prothombin time

PTT: Partial thromboplastin time

QD: daily

Qtc: corrected QT interval

RANO: Response Assessment in Neuro-Oncology Criteria

RNA seq: Ribonucleic acid sequencing

RT: Radiation therapy

SAE: Serious adverse event

SD: Stable disease

$T_{1/2}$: half-life

TEAE: treatment emergent adverse event

TK: toxicokinetic

TMZ: Temozolomide

TRAE: treatment related adverse event

ULN: upper limit of normal

VEGF: Vascular endothelial growth factor

Vss: volume of distribution at steady-state

WHO: World Health Organization

WOCBP: Women of child bearing potential

WT: Body weight

Study Synopsis

Title	*A SINGLE-ARM, OPEN-LABEL, PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF ABEMACICLIB IN PATIENTS WITH RECURRENT OLIGODENDROGLIOMA*
Short Title	Abemaciclib in Recurrent Oligodendroglioma
IRB and Protocol #	IRB#: 832198; UPCC 28318
Study Center	Single-center: University of Pennsylvania
Study Rationale	About 1,000 patients are diagnosed with oligodendroglioma each year in the United States. All undergo standard radiation and alkylating chemotherapy, but the disease recurs uniformly and is incurable. Although the biology of oligodendroglioma has become increasingly well-understood over the past 5-10 years, no new therapies have been developed. The *CIC* gene, which encodes a high-mobility group (HMG) box transcriptional repressor, is mutated in ~70% of oligodendrogliomas and is associated with substantially worse outcomes. Oligodendrogliomas with *CIC* mutations overexpress Cyclin D1 (*CCND1*), which is felt to contribute to their aggressiveness and relatively poor response to standard therapies. CDK4/6 inhibitors, several of which have been approved for metastatic breast cancer, block the interaction of CDK4 and CDK6 with D-type cyclins, thereby inhibiting phosphorylation of retinoblastoma protein and leading to G_1 cell cycle arrest. Abemaciclib is a novel CDK4/6 inhibitor that distributes across the blood-brain barrier and prolongs survival in an intracranial glioblastoma xenograft model. Given its effect on the interaction between Cyclin D1 and CDK4/6 and effective central nervous system penetration, the current protocol uses abemaciclib for the treatment of recurrent oligodendroglioma.

Study drug and duration of administration	Abemaciclib 200mg tablet PO twice daily administered on 28-day cycles Subjects remain on treatment until tumor progression or unacceptable toxicity. Subjects will undergo an MRI of the brain every 8 weeks to assess tumor response or progression.
Objectives	**Primary Objective:** • To determine the efficacy of abemaciclib for recurrent oligodendroglioma, as measured by the estimated proportion of patients alive without disease progression at 6 months from study enrollment (PFS-6) **Secondary Objectives:** • To evaluate the safety and tolerability of abemaciclib in recurrent oligodendroglioma • To estimate the objective radiographic response rate (ORR) associated with abemaciclib in recurrent oligodendroglioma • To determine the median progression-free survival (PFS) and overall survival (OS) of patients with recurrent oligodendroglioma treated with abemaciclib • To determine ORR, PFS, and OS in the subgroup of recurrent oligodendroglioma patients with tumor *CIC* gene mutations **Exploratory Objectives:** • To measure pharmacodynamic markers of abemaciclib activity on oligodendroglial tumor cells • To identify pre-treatment tumor characteristics that are associated with response to abemaciclib recurrent oligodendroglioma • To radiographically assess intratumoral pH of oligodendroglioma and the change in pH induced by treatment with abemaciclib
Endpoints	**Primary Endpoint:** • Progression-free survival status of the subject at 6 months after enrollment, either a) tumor progression (as measured by modified RANO criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors) or death due to disease or toxicity; OR b) alive without tumor progression, i.e., a binary endpoint.

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Secondary Endpoints:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs, and through clinical laboratory evaluations.
- Objective radiographic response (ORR), as measured by modified Response Assessment in Neuro-Oncology (RANO) criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors.
- PFS, defined as the time from date of enrollment until the earliest date of disease progression (as determined by modified RANO criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors) or death due to any cause
- OS, defined as the time from date of enrollment until death from any cause.
- ORR, PFS, and OS will also be measured separately in (1) subjects whose tumors harbor a mutation in the *CIC* gene, and (2) subjects who have received only one line of prior alkylating chemotherapy

Exploratory Endpoints:

- Measurement of post-treatment pharmacodynamic markers of abemaciclib activity in oligodendroglioma, including expression of Ki67, cyclin D1, phosphorylated Rb protein, and topoisomerase II alpha; effects on the immune microenvironment will also be explored
- Association between pre-treatment (archival) tumor genomics, transcriptomics, and proteomics and ORR, PFS, and OS
- Detection of *IDH* and *CIC* mutations and measurement of associated mutant allele fractions in plasma cell-free DNA before and during the course of treatment
- Pre- and post-treatment intratumoral pH by MRI using Chemical Exchange Saturation Transfer (CEST) technique (in patients where this imaging is able to be performed)

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Study Design, Statistics, and Sample Size

Statistical analysis for primary endpoint: The total sample size for this trial is 10 subjects. A single-stage design will be used.

The alternative hypothesis of this study is that the proportion of subjects without an event (progression of disease or death due to disease or toxicity) at 6 months from the time of study enrollment will be 85% or higher. We will test this hypothesis against a null hypothesis of 50% of subjects without an event at 6 months. With 10 subjects, the power to detect this difference is 82%, with a probability of type I error (alpha) of 0.10 (one-sided). The study will be considered positive if 8 or greater subjects are 6-months event-free.

Statistical analyses for additional secondary and exploratory endpoints: Descriptive analyses will be conducted to summarize subject characteristics and detect potential selection bias as a result of missing data or dropout. Variable distributions will be examined; if needed, appropriate transformations will be performed. Kaplan-Meier curves will be generated for PFS and OS. Paired t-tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are normally distributed. Wilcoxon signed-rank tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are not normally distributed. Multiple comparison adjustment using false discovery rate (FDR) will be used.

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1 Background

1.1 Introduction

This document is the clinical research protocol for an open-label, single-institution, single-arm phase II study of the efficacy and safety of abemaciclib in patients with recurrent oligodendroglioma. The described study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations, including 45 CFR 46, 21 CFR Parts 50, 54, 56, and Good Clinical Practice: Consolidated Guidelines approved by the International Conference of Harmonisation (ICH).

The study shall be conducted as described in this approved protocol. The investigator should not implement any deviation or change to the protocol without prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB for review and approval and (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

1.2 Disease Background and Study Rationale

About 1,000 patients are diagnosed with oligodendroglioma each year in the United States. As of the 2016 update of the World Health Organization (WHO) classification of central nervous system tumors, oligodendroglial tumors are now more narrowly defined by molecular diagnostics to include only gliomas harboring both a mutation in isocitrate dehydrogenase type 1 (*IDH1*) or type 2 (*IDH2*) and codeletion of chromosomes 1p and 19q (Louis et al, *Actaneuropathol* 2016). Oligodendroglioma is further classified as low grade (WHO grade II) or high grade (WHO grade III, also known as anaplastic oligodendroglioma), although the management of both grades is similar.

Initial treatment of oligodendroglioma consists of maximal safe surgical resection. In patients with grade III tumors, or for patients with grade II tumors that are considered high risk (residual disease after surgery, age >=40, large preoperative tumor size, and/or elevated MIB-1 index), adjuvant radiation (50-54 Gy) is standard of care. Based on several randomized phase III trials demonstrating a significant overall survival (OS) benefit for the addition of alkylating chemotherapy to adjuvant radiation, chemotherapy is often used concurrently and/or after radiation when radiation is indicated (Shaw et al, *J Clin Oncol* 2012; Cairncross et al, *J Clin Oncol* 2013; Kouwenhoven et al, *Neuro Oncol* 2009; Buckner et al, *N Eng J Med* 2016). Options include temozolomide concurrent with radiation and for 6-12 months after radiation, or PCV x 6 cycles (procarbazine, CCNU, and vincristine). Under this treatment paradigm, median OS approaches ~14-15 years. However, despite the prolonged clinical course seen with oligodendroglioma, these tumors recur uniformly (typically as high-grade tumors), and the outcome is almost always fatal. There are currently no approved therapies for recurrent oligodendroglioma, and treatment is non-uniform across different institutions (Weller et al, *Lancet Oncol* 2017). Options including reoperation, re-irradiation, or repeat courses of systemic cytotoxic chemotherapy (typically temozolomide or a nitrosourea such as CCNU; patients often

receive whichever agent they did not receive as first-line therapy). Regardless, the median OS for recurrent anaplastic oligodendrogioma has been most frequently described as being less than one year (Chinot et al, *J Clin Oncol* 2001; Triebels et al, *Neurology* 2004; Chamberlain et al, *Cancer* 2009). Thus, effective treatment for recurrent oligodendroglioma represents a significant unmet medical need.

The CIC gene, which encodes a high-mobility group (HMG) box transcriptional repressor, is mutated in ~70% of oligodendrogliomas (Bettegowda et al, *Science* 2011; Yip et al, *J Pathol* 2012) and is associated with substantially worse outcomes. Oligodendrogliomas with CIC mutations overexpress cyclin D1 (CCND1), which may contribute to their aggressiveness and relatively poor response to standard therapies (Gleize V et al, Ann Neurol 2015). D-type cyclins, including cyclin D1, assemble with the cyclin-dependent kinases CDK4 and CDK6 to cause phosphorylation of Rb protein and subsequent cell cycle progression from the G1 to the S phase (Ashgar et al, *Nat Rev Drug Discov* 2015). Therapeutic inhibition of CDK4/6 activity, which leads to Rb dephosphorylation and cell cycle arrest, has revolutionized the care of breast cancer and is being studied in many other cancers with CDK4/6-Cyclin D activation (Sherr et al, *Cancer Discovery* 2016).

While there is some rationale for studying CDK4/6 inhibitors for any Rb-positive cancer, it has recently become clear that certain mechanisms of CDK4/6-Cyclin D activation are more likely to lead to sensitivity to CDK4/6 inhibition than others (Gong et al, Cancer Cell 2017). In one elegant study using the CDK4/6 inhibitor abemaciclib in cell lines from many different cancers, the authors demonstrated that the presence of upstream genetic defects known to increase expression of D-type cyclins (termed “D-cyclin activating features” or “DCAF”) are more likely to predict sensitivity to CDK4/6 inhibition compared to direct causes of increased D-type cyclins, such as CCND1 amplification (Gong et al, Cancer Cell 2017). Since oligodendrogliomas with CIC mutations represent DCAF cancers as defined in this manner, and because CIC mutations are found in the majority of oligodendrogliomas and portend a worse prognosis, this represents a highly logical population in which to study CDK4/6 inhibition. Loss of cyclin D1 and CDK4 impeded progression to higher grades of malignancy in a mouse model of oligodendroglioma, further strengthening the “driver” role of the CDK4/6-cyclin D1axis in this disease (Ciznadija D et al, Cancer Res 2011).

Abemaciclib (LY2835219) is a selective and potent small molecule inhibitor of CDK4 and CDK6 with broad antitumor activity in preclinical pharmacology models. Abemaciclib is approved by the FDA 1) in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy, and 2) as monotherapy for the treatment of adult patients with HR positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. Abemaciclib is structurally distinct from other dual CDK4/6 inhibitors (such as palbociclib and ribociclib), resulting in greater selectivity for CDK4 compared with CDK6 and significantly better blood-brain-barrier penetration (Gelbert LM et al, Invest New Drugs 2014; Raub TJ et al, Drug Metab Dispos 2015; Sahebjam S et al, J Clin Oncol 2016). In nonclinical species, abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors. As a result of its brain exposure,

treatment with abemaciclib in a rat orthotopic brain tumor model produces statistically significant and dose-dependent improvement in survival.

Based on the significant upregulation of cyclin D1 in *CIC*-mutant oligodendroglioma and the brain-penetrant properties of abemaciclib, the following protocol has been developed as a phase II study of abemaciclib in patients with recurrent oligodendroglioma. Even in the minority of oligodendrogliomas that do not harbor a *CIC* mutation, abemaciclib may still have anti-tumor activity. This is based on preclinical data suggesting significant inhibition of tumor growth using abemaciclib as monotherapy in human xenograft models of glioblastoma, the most aggressive of high grade gliomas. Thus, the current study will allow for subjects with recurrent oligodendroglioma regardless of (and without pre-treatment testing for) *CIC* mutation. However, the study is likely to be enriched for patients whose tumors harbor this mutation based on its high prevalence is recurrent/high-grade oligodendroglioma. Tumor testing for *CIC* mutation will only occur after subjects have been enrolled and will not impact study treatment.

1.3 Name and Description of Study Products

1.3.1. Abemaciclib

Abemaciclib (formerly LY2835219) represents a selective and potent small molecule CDK4 and CDK6 dual inhibitor with broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non–small cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 mg/kg to 100 mg/kg following daily oral administration for 21 to 28 days. Additional nonclinical studies in xenograft models for human NSCLC and melanoma also show that abemaciclib may be used in combination with standard cytotoxic or targeted therapies to improve efficacy of these agents.

In nonclinical species, abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors as well as cancers that have metastasized to the brain. As a result of its brain exposure, treatment with abemaciclib in a rat orthotopic brain tumor model produces statistically significant and dose-dependent improvement in survival.

Abemaciclib demonstrates moderate-to-high bioavailability in preclinical species. In repeat-dose toxicokinetic studies, abemaciclib showed generally dose-dependent exposure with no gender differences. Abemaciclib is highly metabolized, and hepatic elimination plays a major role in the clearance of abemaciclib and its metabolites in rat, dog, and human. 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).

In preclinical species, the primary target organs for toxicity (associated with up to 3 months of continuous daily dosing) are bone marrow (resulting in pancytopenia), gastrointestinal tract,

lymphoid tissues, and male reproductive tract. All of these changes demonstrated complete or partial reversibility during the recovery period. In humans, the most common (≥10%) treatment-emergent adverse events (TEAEs) possibly related to study drug for solid tumor patients who received single-agent abemaciclib include diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, leukopenia, thrombocytopenia, anemia, abdominal pain, and blood creatinine increased. Increased rates of skeletal and cardiac variations and malformations, accompanied by decreased fetal weights, were observed in an embryo-fetal development study of abemaciclib in rats.

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.

Complete, detailed nonclinical and clinical data for abemaciclib, including complete pharmacology, toxicology, and genotoxicity data, is available in the Investigator's Brochure.

1.3.2. 1p/19q codeletion testing

Whole-arm deletion of 1p and 19q, due to an unbalanced translocation between chromosomes 1 and 19, is a defining feature of oligodendroglial tumors according to the World Health Organization (WHO) 2016 Classification of Central Nervous System Tumors (Louis, *Acta Neuropathol* 2016). Because this is the tumor type for which abemaciclib is being studied in this protocol, the presence of whole-arm deletion of both 1p and 19q (i.e., "1p/19 codeletion") is required as an inclusion criteria for enrollment in this study. Combined whole-arm loss of 1p and 19q is invariably associated with IDH mutation. Therefore, confirmation of IDH mutation (another defining feature of oligodendroglioma) is not mandated for this protocol.

Testing for codeletion of 1p and 19q is performed in clinical practice on all grade II or III gliomas (unless tumors have clear evidence of TP53 or ATRX mutations, in which case the diagnosis of oligodendroglioma is exceedingly unlikely) (Louis, *Acta Neuropathol* 2016). Most diagnostic laboratories assess 1p/19 status using fluorescence in situ hybridization (FISH), since this technique provides information on chromosomal losses, polysomies, and intratumoral variation. However, genomic sequencing or methylomic analyses are also used.

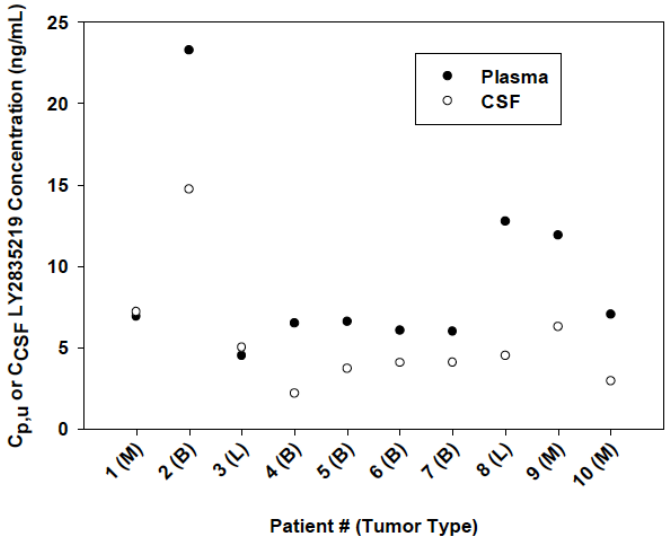
Acceptable methods for determination of the 1p/19q loss for eligibility determination for this protocol will include FISH, genomic sequencing, or methylomic analyses. The laboratory where this testing is performed must be Clinical Laboratory Improvement Act (CLIA) certified.

1.4 Dose and schedule rationale

Subjects will be treated with abemaciclib 200mg by mouth once every 12 hours. Dosing will be continuous and administered on a 28-day cycle. This dose is the previously defined maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for abemaciclib as a single agent. This is also the FDA approved dose for use as monotherapy for adults with HR-positive, HER2-negative advanced/metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy. Lastly, this dose was also administered to 10 patients with brain

metastases in study JPBO and demonstrated to result in cerebrospinal fluid (CSF) drug concentrations consistent with unbound plasma concentrations (**Figure 1)**.

Figure 1. Relationship between time-matched cerebrospinal fluid and unbound plasma concentrations in Study JPBO (abemaciclib 200mg twice daily by mouth).



Abbreviations: CSF = cerebrospinal fluid; C_{CSF} = drug concentration in CSF; $C_{p,u}$ = unbound drug concentration in plasma; B = breast cancer; L = non–small-cell lung cancer; M = melanoma.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1. Primary Objective:

- To determine the efficacy of abemaciclib for recurrent oligodendroglioma, as measured by the estimated proportion of patients alive without disease progression at 6 months from study enrollment (PFS-6)

2.1.2. Secondary Objectives:

- To evaluate the safety and tolerability of abemaciclib in recurrent oligodendroglioma
- To estimate the objective radiographic response rate (ORR) associated with abemaciclib in recurrent oligodendroglioma
- To determine the median progression-free survival (PFS) and overall survival (OS) of patients with recurrent oligodendroglioma treated with abemaciclib
- To determine ORR, PFS, and OS in the subgroup of recurrent oligodendroglioma patients with tumor *CIC* gene mutations

2.1.3. Exploratory Objectives:

- To measure pharmacodynamic markers of abemaciclib activity on oligodendroglial tumor cells

- To identify pre-treatment tumor characteristics that are associated with response to abemaciclib recurrent oligodendroglioma
- To radiographically assess intratumoral pH of oligodendroglioma and the change in pH induced by treatment with abemaciclib

2.2. Study Endpoints

2.2.1. Primary Endpoint:

- Progression-free survival status of the subject at 6 months after enrollment, either a) tumor progression (as measured by modified RANO criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors) or death due to disease or toxicity; OR b) alive without tumor progression, i.e., a binary endpoint.

2.2.2. Secondary Endpoints:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of adverse events (AEs) through physical examinations, by evaluating changes in vital signs, and through clinical laboratory evaluations.
- Objective radiographic response (ORR), as measured by modified Response Assessment in Neuro-Oncology (RANO) criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors.
- PFS, defined as the time from date of enrollment until the earliest date of disease progression (as determined by modified RANO criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors) or death due to any cause
- OS, defined as the time from date of enrollment until death from any cause.
- ORR, PFS, and OS will also be measured separately in (1) subjects whose tumors harbor a mutation in the *CIC* gene, and (2) subjects who have received only one line of prior alkylating chemotherapy

2.2.3. Exploratory Endpoints:

- Measurement of post-treatment pharmacodynamic markers of abemaciclib activity in oligodendroglioma, including expression of Ki67, cyclin D1, phosphorylated Rb protein, and topoisomerase II alpha; effects on the immune microenvironment will also be explored
- Association between pre-treatment (archival) tumor genomics, transcriptomics, and proteomics and ORR, PFS, and OS
- Detection of *IDH* and *CIC* mutations and measurement of associated mutant allele fractions in plasma cell-free DNA before and during the course of treatment
- Pre- and post-treatment intratumoral pH by MRI using Chemical Exchange Saturation Transfer (CEST) technique (in patients where this imaging is able to be performed)
-

3 INVESTIGATIONAL PLAN

3.1. General Design

This is a single-center, phase II, single-arm, open label study evaluating the efficacy and safety of abemaciclib for patients with recurrent oligodendroglioma (molecularly defined per the WHO 2016 guidance, i.e., presence of IDH mutation and 1p19q codeletion). The study will enroll 10 subjects who are evaluable for the study's primary endpoint (subjects must be receive at least one dose of abemacicilb to be evaluable for the primary endpoint). The study will be stratified by number of lines of prior alkylating chemotherapy (one prior line versus two or more prior lines). Eligibility criteria are such that of the 10 total subjects enrolled, at least 2 must have had only one prior line of alkylating chemotherapy.

The study consists of a screening phase, study intervention/treatment phase, and a follow-up phase.

3.1.1. Screening Phase

Subjects will be recruited from the Medical Oncology, Radiation Oncology, and Neurosurgery practices at the University of Pennsylvania Health System. The treating physician will determine if the patient is a potential research candidate and has the capacity to consent. The treating physician will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating physician will contact a qualified member of the research team in the Neurosurgery Clinical Research Division at the University of Pennsylvania and request availability for enrollment. A qualified member of the research team will continue the formal consent process. This person will explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study before making her decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which screening procedures will be performed. Subject eligibility will be evaluated based upon the criteria outlined in the protocol. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator. All members of the research team will have successfully completed patient oriented research training.

3.1.2. Study Intervention Phase

After enrollment, subjects will initiate treatment with abemaciclib 200mg by mouth once every 12 hours. Continuous dosing will occur on 28-day treatment cycles. Full study procedures are outlined in ***Section 6.*** Subjects will continue on abemaciclib until study drug discontinuation criteria are met, as defined in ***Section 5.***

3.1.3. Follow Up Phase

Any subject who permanently discontinues study drug for any reason outlined in ***Section 5.8*** will proceed to follow-up.

3.1.3.1. Safety Follow-Up

The safety follow-up period is the interval between the last dose of abemaciclib and the scheduled safety follow-up visit(s), which occurs 28 (+/- 7) days after the EOT visit. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period. If the subject cannot return to the site for the safety follow-up visit, the subject is contacted by telephone for collection of AEs and SAEs, and this should be documented in the eCRF.

3.1.3.2. Disease Status Follow-Up

Subjects who discontinue abemaciclib for a reason other than disease progression are assessed by radiologic imaging to monitor disease status. These assessments occur every 10 weeks (± 14 days). Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of the study.

3.1.3.3. Survival Follow-Up

Subjects are contacted by telephone, e-mail, or visit every 12 weeks from the last dose of abemaciclib to capture survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Public records/databases are searched if contact with the subject is lost.

3.2 Replacement of Subjects

Any subject who is enrolled onto the study but meets one of the following criteria is replaced by enrollment of a new subject:

- The subject is enrolled, but never receives a dose of abemaciclib
- The subject starts abemaciclib, but becomes pregnant (and therefore is taken off abemaciclib per study drug discontinuation criteria ***Section 5.8***) before the first response evaluation (MRI) occurs
- The subject starts abemacicilb, but consent is withdrawn by the subject before the first response evaluation (MRI) occurs
- The subject starts abemaciclib, but is subsequently found not to have met eligibility criteria, AND the medical monitor, in collaboration with the investigator, determined that the subject should be withdrawn from the study, AND the first response evaluation (MRI) has not yet taken place
- The subject starts abemaciclib, but is then noncompliant with study procedures or abemaciclib administration in the investigator's opinion, AND the sponsor has been consulted and has determined that the subject should be withdrawn from the study, AND the first response evaluation (MRI) has not yet taken place

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As long as the subject has not withdrawn his/her consent, the non-treated (replaced) subject is followed for safety follow-up per **Table 7.** All safety-related data collected for replaced subjects is still included in analysis of study safety endpoints. However, the subject is not included in the primary endpoint efficacy analysis (see ***Section 8 Statistical Plan***). Subject replacement occurs up to and no more than 5 times (i.e., up to 15 subjects can be enrolled to obtain 10 subjects who receive abemaciclib).

3.3. Duration of Study Participation

After signing the ICF, screening procedures commence. Each enrolled subject begins treatment with abemaciclib. Treatment continues until the subject meets any one or more of the criteria for study drug discontinuation (see ***Section 5.8; Study Drug Discontinuation Criteria***). When a subject discontinues abemaciclib, but has not withdrawn consent, the subject enters the follow-up period.

3.4. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued study drug and have completed applicable safety follow-up assessments.

In addition, the sponsor may terminate the study if required by regulatory decision, or upon review of emerging data.

3.5 Total Number of Subjects and Sites

This is a single center study and subjects are only recruited from the University of Pennsylvania. Recruitment ends when 10 subjects have received at least one dose of abemaciclib. Due to drop-out between enrollment and receipt of the first dose of abemaciclib, although it is expected to be an infrequent event, up to 15 total subjects may be enrolled to obtain the desired sample size of 10 treated subjects.

4. SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1.Histologically and molecularly confirmed diagnosis of oligodendroglioma according to 2016 WHO Classification (tumor tissue must show co-deletion of chromosomes 1p and 19q, referred to as “1p/19q codeletion”).

- Acceptable methods for determination of 1p/19q codeletion include fluorescent in situ hybridization (FISH), genomic sequencing, or methylomic analyses; testing must have been performed in a CLIA certified laboratory.

Tumors may have been either grade II or grade III at time of initial diagnosis.
2. Oligodendroglioma must be progressive or recurrent following BOTH a) prior radiation therapy and b) at least one prior line of alkylating chemotherapy.

- Both previous radiotherapy and chemotherapy could have been received as initial adjuvant therapy or for previous recurrences, and both previous radiotherapy and chemotherapy could have been used when the tumor was grade II.

3. Patients may have had treatment for an unlimited number of prior relapses. Recent surgical resection for recurrence is allowed.

4. Patients must have recovered from severe toxicity of prior therapy. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE v. 5.0] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or grade 2 peripheral neuropathy prior to enrollment. The following intervals from previous treatments are required to be eligible:

- 12 weeks from the completion of radiation
- 6 weeks from a nitrosourea cytotoxic chemotherapy
- 3 weeks from a non-nitrosourea cytotoxic chemotherapy
- 4 weeks from any investigational (not Food and Drug Administration [FDA]-approved for glioblastoma) agents, or within a time interval less than at least 5 half-lives of the investigational agent whichever is shorter".

5. Patients must be able to swallow oral medications

6. Age 18 or older

7. Karnofsky performance status >= 60

8. Life expectancy >3 months

9. Adequate hematologic parameters, including:
- Absolute neutrophil count >= 1,500/ul
- Platelets >= 100,000/ul
- Hemoglobin >= 8 g/dl. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.

10. Adequate hepatic function within 7 days prior to enrollment, defined as follows
- Total bilirubin ≤ 1.5 x ULN (patients with Gilbert's Syndrome with a total bilirubin ≤ 2.0 mg/dl and direct bilirubin within normal limits are permitted)
- ALT and AST ≤ 3x upper limit of normal (ULN)

11. Adequate renal function within 7 days prior to enrollment, defined as follows:
- serum creatinine <=1.5 x institutional ULN OR calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or CrCl) >=50 mL/min for subjects with creatinine levels >1.5x institutional ULN

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4.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Prior treatment with a CDK4/6 inhibitor

2. Patients must not be on enzyme-inducing anti-epileptic drugs (EIAEDs; carbamazepine, phenytoin, and phenobarbitol)

3. The patient has serious preexisting medical condition(s) that would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea)

4. Females who are pregnant or lactating are excluded.
   - If a female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a medically approved contraceptive method during the treatment period and for 3 months following the last dose of abemaciclib.
   - If a male, agree to use a reliable method of birth control and to not donate sperm during the treatment period and for at least 3 months 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.
   - Women must agree not to breast feed while on abemaciclib treatment and for at least three months following the last dose of study therapy.

5. The patient has active bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C). Patients with known HIV infection are excluded given the potential for interactions between antiretroviral agents and abemaciclib. Patients with known Hepatitis B or Hepatitis C infection are excluded only if there is evidence of active infection (detectable Hepatitis B surface antigen, detectable Hepatitis C RNA). For patients without known viral hepatitis or HIV infection, viral hepatitis and HIV testing are NOT required to determine eligibility for this trial.

6. The patient has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.

7. Subjects with major medical, neurologic or psychiatric condition who are judged as unable to fully comply with study therapy or assessments should not be enrolled.

8. Prisoners or subjects who are involuntarily incarcerated are excluded.

9. Subjects who are compulsorily detained for treatment of either a psychiatric or physical

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(eg, infectious disease) illness are excluded
10. Subjects requiring concurrent administration of any other anticancer agents including chemotherapy and biologic agents (such as bevacizumab) or the use of other concurrent investigational treatment drugs and/or devices

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

5. TREATMENT

5.1. Description of Study Drug

Abemaciclib is a kinase inhibitor for oral administration. It is a white to yellow powder with the empirical formula C27H32F2N8 and a molecular weight 506.59. The chemical name for abemaciclib is 2-Pyrimidinamine, N-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4 fluoro-2-methyl-1-(1-methylethyl)-1H-benzimidazol-6-yl].

Abemaciclib tablets are provided as immediate-release oval white, beige, or yellow tablets. Inactive ingredients are as follows:

Excipients—microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide.
Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

The starting dose for this trial is 200mg twice daily and can be reduced for toxicity according to the guidance in ***Section 9.*** Only the following dosage form and strength is available for this study:

- 50 mg tablets.

5.2. Packaging and labeling of investigational agent

Abemaciclib tablets are supplied for this study in 50mg blister packs that will be labeled as “For Investigational Use Only”.

5.3. Receipt of Investigational Agent

Abemaciclib tablets are supplied by Eli Lilly to:
Penn Investigational Drug Service
3600 Spruce St, Ground Maloney Building
Philadelphia, PA 19104

5.4 Storage of study drug

Abemaciclib tablets are stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

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5.5. Preparation/Administration and Accountability

Abemaciclib tablets will be dispensed to subjects at their office visit on Day 1 of each 28 day cycle. Subjects should be counseled by the investigator to maintain strict adherence to the study regimen as prescribed and to keep a pill diary to record all doses of abemaciclib that are taken or missed. The administration of study drug should be recorded in the appropriate sections of the eCRF. The study drug provided for this study will be used only as directed in the study protocol.

5.6. Subject Compliance Monitoring

Treatment compliance is monitored by drug accountability. Each subject will be instructed to bring all blister packs of study drug at Day 1 study visits, at which time compliance is assessed (see ***Section 6 Study Procedures*** *3* for full study schedule). Subjects will also keep a pill diary to record all abemaciclib doses taken or missed at home.

5.7. Concomitant Medications:

1) In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the subject records and on the appropriate case report form. This includes corticosteroids of any dosage for the management of brain edema related to the tumor and/or study drugs. The administration of any other anticancer agents including chemotherapy and biologic agents (such as bevacizumab) is NOT permitted. Similarly, the use of other concurrent investigational drugs is not allowed.

2) List of medications that are prohibited during this study:

- Any anticancer medications, including chemotherapy or biologic therapy other than the study medications.
- Any immunological-based treatment for any reason, with the exception of corticosteroids
- Radiation therapy

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

3) 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.

CYP3A inducers
Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors
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.

5.8. Study Drug Discontinuation Criteria

Subjects **must** be discontinued from abemacicilb for the following reasons:

• The subject becomes pregnant
• Consent is withdrawn by the subject

Note: Consent withdrawn means that the subject can no longer be followed and no additional data can be collected. Subjects may choose to discontinue abemaciclib and remain in the study to be followed for progression and survival.

• Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment
• Confirmed radiographic progression of disease per modified RANO criteria (***Section 7***).
• The subject has an unacceptable toxicity, defined as any one of the following:
    - An AE requiring more than 3 dose reductions
    - Persistent AE requiring a delay of therapy for more than 4 weeks (28 days) unless a greater delay has been approved by the Principal Investigator
    - Concurrent elevation of ALT > 3 × ULN and total bilirubin > 2 × ULN in subjects who do not have evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevations
    - Grade 4 ALT elevation
    - Occurrence of any AE that is related to treatment with the study drug that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest
• The study is terminated by the sponsor
• The study is terminated by the IRB

A subject **may** be discontinued from abemaciclib as follows:

• If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
• If a subject is noncompliant with study procedures or abemaciclib administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the subject.

Reasons and procedures for replacing subjects are detailed in ***Section 3.2 Replacement of Subjects.***

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5.9 Management of Study Drug Toxicities and Dose Reductions

5.9.1. Guidelines for Diarrhea Management

Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea.

At enrollment, subjects 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.

Refer to **Table 1** for additional information for diarrhea management and dose modification.

Table 1: Dose Modification and Management- Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide.	
CTCAE Grade (v 5.0)	**Abemaciclib Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	

Dose level reductions should be made in 50 mg increments. *For example, with the starting dose of abemaciclib for this study of 200 mg q12 hours, dose reduction 1 would be 150 mg q12 hours, dose reduction 2 would be 100 mg q12 hours.*

5.9.2. 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.

5.9.3. General Guidance for Hepatic Monitoring

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation are possible with the use of abemaciclb. Transaminitis should be managed according to the guidance in **Table 2.**

Table 2: Dose Modification and Management — Increased ALT/AST

CTCAE Grade (v 5.0)	Abemaciclib Dose Modifications
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 2 (>3.0 x ULN) with total bilirubin >2x ULN, in the absence of cholestasis	Discontinue abemaciclib
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT/AST 5×ULN and elevated TBL 2×ULN, or ALT/AST 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.

Table 3: Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper

	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
	Immunoglobulin IgA (quantitative)
Serology	
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [c]	Anti-actin antibody [b]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [c]	EBV DNA [c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
	Liver kidney microsomal type 1 (LKM-1) antibody
Microbiology	
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.
[b] Not required if anti-smooth muscle antibody (ASMA) is tested.
[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

5.9.4. 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. Hematologic toxicity should be managed according to the guidance in **Table 4.**

Table 4: Dose Modification and Management — Hematologic Toxicities

CTCAE Grade (v 5.0)	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.
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.

5.9.5. General Guidance for Nonhematologic Toxicities (excluding diarrhea,increased ALT/AST, and ILD/Pneumonitis) Monitoring

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

5.9.6. General Guidance for Interstitial Lung Disease (ILD)/Pneumonitis

Interstitial lung disease (ILD) /pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and ask your patients to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high resolution computed tomography, broncheoalveolar lavage, and biopsy as clinically indicated. Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis.
(see also Table 6: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

Table 6: Dose Modification and Management – Interstitial Lung Disease/Pneumonitis

CTCAE Grade (v 5.0)	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue Abemaciclib

5.10 Return of Investigational Products

Study drug containers should not be destroyed. No study drug is returned to Eli Lilly until quality assurance functions are completed with Sponsor approval.

6 SCHEDULE OF STUDY ASSESSMENT AND PROCEDURES

Table 6: *Schedule of Study Procedures, SCREENING AND INTERVENTION*

Study Week	Screening	W1-2	W3-4	W5-6	W7-8	W9	W13	Q 4 weeks	Q 8 weeks	EOT
Cycle# (28-day cycles)		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle X	Duration of study	
Day (and window)	-21 to 1	1±2	15±3	1±2	15±3	1±2	1±2	1±2	1±3	
Informed Consent	X									
Review Inclusion/Exclusion Criteria (Section 4)	X									
Karnofsky Performance Status (Section 7)	X	X	X	X		X	X	X		
Demographics/Medical History (Section 7)	X									
Physical Assessment (targeted after screening visit) (Section 7)	X	X	X	X		X	X	X		X
Vital Signs: BP, HR, RR (Section 7)	X	X	X	X		X	X	X		X
Weight (Section 7)	X	X	X	X		X	X	X		X
Height (Section 7)	X									

Pregnancy Test (Section 7; within 7 days of first dose of study drug)	X									X
Concomitant Medications (Section 7)	X	X	X	X	X	X	X	X		X
Clinical Laboratory Evaluation (Section 7)	X		X	X	X	X	X	X		X
Blood collected for correlatives (Section 7)		X		X						X
Adverse Event / Unanticipated Problems Assessment (Section 7)	X	X	X	X		X	X	X		X
MRI brain (tumor assessment by RANO criteria) (Section 7)*	X**					X**			X*	
Abemaciclib pill reconciliation and/or dispensation (Section 5)		X		X		X	X	X		X
Phone call to monitor proper abemaciclib use at home (Section 7)		X (during W2)								

* MRI scans are typically performed once every 8 weeks on study. However, if a scan demonstrates preliminary progressive disease, as defined according modified RANO criteria (***Section 7.6 Efficacy Evaluations***) for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors, the subsequent MRI may be performed between 4 and 8 weeks from the first MRI demonstrating preliminary progressive disease (exact timing left to Investigator discretion)
**

Table 7*: *Schedule of study procedures, FOLLOW-UP

Procedure	**Safety**	**Disease Status**	**Survival**
	28 d after EOT (+/- 7 d)	**Q10W after EOT (+/- 14d)**	**Q12W (+/- 7d)**
Karnofsky Performance Status (Section 7)	X		
Targeted Physical Assessment (Section 7	X		
Vital Signs: BP, HR, RR, weight (Section 7)	X		

Prior/Concomitant Medications (Section 7)	X		
Clinical Laboratory Evaluation (Section 7)	X		
Adverse Event / Unanticipated Problems Assessment (Section 7)	X		
MRI brain (tumor assessment) (Section 7)		X	
Subject Vital Status (Collection of survival information every 3 months until death, lost to follow-up, or withdrawal of study consent)	X		X

6.1 Unscheduled Visits

During the conduct of the study, there are multiple situations that may require the subject to come to the research site for an unscheduled visit. Reasons for an unscheduled visit include but are not limited to the following:

- Subject missed the visit window
- Subject experienced an AE and needed to be seen for follow-up
- Due to lab results, the investigator has determined that for the welfare of the subject, she or he should be seen sooner than previously scheduled

The data from these visits will be recorded just as any study visit. Depending on the circumstances, the investigator will determine what types of procedures and services need to be conducted.

6.2. Subject Withdrawal from the Study

Subjects may withdraw consent for the study at any time for any reason without impact to their care. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment in the study is inappropriate, lack of adherence to the intervention or study procedures or visit schedules, the study plan is violated, or for administrative and/or other safety reasons. It is documented whether or not each subject completes the clinical study. If the subject actively withdraws consent for collection of follow-up data (ie, subsequent anticancer treatments, safety follow-up, and survival), then no additional data collection occurs; however, all subjects are informed of the option to discontinue treatment and/or study assessments but allow collection of information in the follow-up period of the study. In the event that the latter occurs, the end-of-treatment (EOT) visit should be conducted (see **Table 6** for EOT visit procedures). Thereafter, the subject will return for follow-up visits for safety and disease/survival status, with procedures as outlined above in **Table 7.**

If a subject withdraws from the study and has not yet received a dose of study drug, that subject is replaced according to the procedure outlined in ***Section 3.2; Replacement of Subjects***.

7 CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1 Demographic and Medical Record Review

The following variables are collected at screening and abstracted from the electronic medical chart:

Date of birth

Height

Weight

Medical History, Prior and Concomitant Medications, and Allergies

-All concomitant medications must be recorded, and any medication received within 30 days before screening must be recorded.

-Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period.

Karnofsky Performance Status

7.2 Physical Assessment

Physical assessments are performed according to the assessment schedules.

Full physical assessments include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal, musculoskeletal (including spine and extremities), neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height is measured at Screening only. Targeted physical assessments are utilized by the investigator and/or research nurse on the basis of clinical observations and symptomatology. Clinically notable abnormalities that are considered clinically significant in the judgement of the investigator are to be reported as AEs.

7.3 Vital Signs

Height is captured at screening only. Weight is captured according to the Study Schedule (**Table 6**) and as clinically indicated at any other time.

Vital signs (BP, pulse, temperature, and respiratory rate) are captured according to the assessment schedules (**Table 6).** Any changes in vital signs are recorded as an AE, if applicable. Body temperature: Body temperature is measured in degrees Celsius at the times indicated in the Study Schedule (**Table 6**).

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7.4 Clinical Laboratory Evaluations

Blood sampling for the tests in **Table 8** is performed for the following laboratory evaluations according to the schedule outlined in **Table 6:**

- Hematology
- Chemistry and Liver Function
- Additional electrolytes

Table 8: Clinical Laboratory Tests

Category	*Tests*
Hematology	*RBC, hemoglobin, hematocrit, platelet count, WBC with differential*
Chemistry and Liver function tests (comprehensive metabolic panel)	*Basic metabolic panel, SGOT/AST, SGPT/ALT, total Bilirubin*
Additional electrolytes	*Magnesium, phosphorus*

7.5 Pregnancy Testing

WOCBP are required to have a negative serum pregnancy test within 7 days of the first dose of abemaciclib. Pregnancy testing will be performed as outlined in **Table 6**; this includes the EOT visit, although a pregnancy test is not required if a subject is going to hospice. Urine pregnancy tests will be conducted during the intervention phase of the study only as medically indicated. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study. A serum pregnancy test should also be repeated at the EOT visit.

7.6 Efficacy Evaluations

In patients with measurable (1cm x 1cm or greater) enhancing tumors, modified Response Assessment in Neuro-Oncology (RANO) criteria (Ellingson et al, Neurotherapeutics 2017) will be used to assess for tumor response and progression, with definitions as outlined below. For patients with non-enhancing tumors, RANO low grade glioma criteria will be used (van den Bent, Lancet Oncology 2011).

MRI scans will be performed no less frequently than every 8 weeks, but may be performed as frequently as every 4 weeks at the discretion of the investigator. MRIs will be interpreted by the attending neuro-radiologist at the University of Pennsylvania assigned as a sub-investigator on this study.

Measurable disease should be defined as contrast enhancing lesions with a minimum size of *both* perpendicular measurements greater than or equal to 10mm. For example, if the largest diameter is 15 mm but the perpendicular diameter is 8 mm, this would constitute *non-measurable disease*. Up to a total of five target measurable lesions should be defined and ranked from largest to smallest. Non-measurable disease should be defined as lesions that are too small to be measured (less than 1 cm in both perpendicular dimensions), lesions that lack contrast enhancement (non-enhancing disease), or lesions that contain a poorly defined margin that cannot be measured or segmented with confidence.

For patients with measurable, enhancing tumors, the following definitions for disease response and progression will be used according to modified RANO criteria:

***Complete Response* (*CR*): Requires *all* of the following:**
1. Disappearance of all enhancing measurable and non-measurable disease. The first scan exhibiting disappearance of all enhancing measurable and non-measurable disease is considered "preliminary CR". If the second/subsequent scan exhibits measurable enhancing disease with respect to the "preliminary CR" scan, then the response is not sustained, noted as pseudoresponse, PsR, and is now considered "preliminary PD" (note confirmed PD requires at least two sequential increases in tumor volume). If the second scan continues to exhibit disappearance of enhancing disease or emergence of non-measurable disease (less than 10mm bidimensional product), it is considered a *durable CR* and the patient should continue on therapy until confirmed PD is observed.

2. Patients must be off corticosteroids (or on physiologic replacement doses only).

3. Stable or improved clinical assessments

***Partial Response* (*PR*): Requires *all* of the following:**
1. ≥50% decrease in sum of products of perpendicular diameters or ≥65% decrease in total volume of all measurable enhancing lesions compared with baseline. The first scan exhibiting ≥50% decrease in sum of products of perpendicular diameters or ≥65% decrease in total volume of all measurable enhancing lesions compared with baseline is considered "preliminary PR". If the second/subsequent scan exhibits PD with respect to the "preliminary PR" scan, then the response is not sustained, noted as pseudoresponse, PsR, and is now considered "preliminary PD" (note confirmed PD requires at least two sequential increases in tumor volume). If the second/subsequent scan exhibits SD, PR, or CR with respect to the first scan that demonstrated PR, it is considered a *durable PR* and the patient should continue on therapy until confirmed PD is observed.

2. Steroid dose should be the same or lower compared with baseline scan.

3. Stable or improved clinical assessments.

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***Progressive Disease (PD)* is defined by any of the following:**

1. At least 2 sequential scans separated by ≥4 weeks both exhibiting ≥25% increase in sum of products of perpendicular diameters of enhancing lesions. The first scan exhibiting ≥25% increase in sum of products of perpendicular diameters of enhancing lesions should be compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response (on stable or increasing steroid dose) and is noted as "preliminary PD." If the second scan at least 4 weeks later exhibits a subsequent ≥25% increase in sum of products of perpendicular diameters of enhancing lesions relative to the "preliminary PD" scan it is considered "confirmed PD" and the patient should discontinue therapy (and the date of confirmed progression should be noted as the scan at which the potential progression was first identified). If the second scan at least 4 weeks later exhibits SD or PR/CR, this scan showing "preliminary PD" is noted as "pseudo-progression", PsP, and the patient should continue on therapy until a second increase in tumor size relative to the PsP scan is observed. Note that any new *measurable* (>10mm x 10mm) enhancing lesions should *not* be immediately considered PD, but instead should be added to the sum of bidimensional products representing the entire enhancing tumor burden.

2. In the case where the best response demonstrates no measurable enhancing disease (visible or not visible), then any new *measurable* (>10mm x 10mm) enhancing lesions are considered PD *after* confirmed by a subsequent scan ≥4 weeks exhibiting ≥25% increase in sum of products of perpendicular diameters of enhancing lesions relative to the scan first illustrating new measurable disease. The first scan exhibiting new measurable disease is noted as "preliminary PD." If the second scan at least 4 weeks later exhibits a subsequent ≥25% increase in sum of products of perpendicular diameters of enhancing lesions relative to the "preliminary PD" scan it is considered "confirmed PD" and the patient should discontinue therapy. If the second scan at least 4 weeks later exhibits SD, CR, PR, or becomes non-measurable, this scan showing "preliminary PD" is noted as "pseudo-progression", PsP, and the patient should continue on therapy until a second increase in tumor size relative to the "preliminary PD", or PsP, scan is observed. Note that any new *measurable* (>10mm x 10mm) enhancing lesions on the subsequent scan following the preliminary PD scan should *not* be immediately considered confirmed PD, but instead should be added to the sum of bidimensional products representing the entire enhancing tumor burden.

3. Clear clinical deterioration not attributable to other causes apart from tumor (e.g. seizures, medication adverse effects, therapy complications, stroke, infection) or attributable to changes in steroid dose. Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. Neurological exam data should be provided to the neuroradiologist as "stable, better, worse" in case report forms or from study sponsor. Clinical status should be recorded as "worse" if the neurological exam is worse, otherwise the clinical status should be set to "not worse." In the event that necessary clinical data is not available, clinical status should be recorded as "not available" and that particular time point can only be reviewed for PD (otherwise "non-evaluable"). Neurological data must be within ±7 days of the time-point response date, otherwise the data is considered "not available". Steroid use should be derived from the concomitant medications on the case report forms and recorded as "Yes", "No", or "not available". A value of "No" should be assigned if, at the time-point, the subject is not on steroids or on physiologic replacement doses only (<1.5 mg dexamethasone or equivalent per day). Steroid dose should be derived from the concomitant medications on the case report forms. Average steroid dose no greater than 2 mg change from baseline should be abstracted to

"stable". If outside this range the steroid dose should be abstracted to "increased" or "decreased" accordingly. Steroid data should be within ±5 days of the time-point response date, otherwise the data is considered "not available".

4. Failure to return for evaluation as a result of death or deteriorating condition.

***Stable Disease* (*SD*): Requires *all* of the following:**

1. Does not qualify for CR, PR, or PD as defined above.

2. In the event that corticosteroid dose was increased (for new symptoms/signs) without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

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Overall Objective Status:

For patients with measurable enhancing tumors, the overall objective status for an evaluation should be determined by combining the subject's radiographic response on target lesions, new disease, neurological status, and steroid dose/usage as defined in **Table 9:**

Table 9. Guidance for establishing overall objective status

Target lesions (current scan)	**Target lesions (previous scan)**	**New sites of measurable disease[a]**	**Neurological status**	**Steroid usage**	**Steroid dose**	**Overall objective status**
CR	Not Evaluated	No	Stable/Better	No	N/A	Preliminary CR
PR	Not Evaluated	No	Stable/Better	Any	Stable/Decreasing	Preliminary PR
PD	Not Evaluated	Yes or No	Stable/Better	Any	Stable/Increasing	Preliminary PD
PD	Preliminary or Confirmed PR/CR	No	Stable/Better	Any	Stable/Increasing	Preliminary PD
SD	Preliminary or Confirmed CR/PR or SD/NE	No	Stable/Better	Any	N/A	SD
PR	Preliminary PR	Yes or No	Stable/Better	Any	Stable/Decreasing	Confirmed PR
SD	Preliminary PR	Yes or No	Stable/Better	Any	Stable/Decreasing	SD (Preliminary PR →Confirmed PR)
SD	Preliminary CR	Yes or No	Stable/Better	Any	Stable/Decreasing	SD (Preliminary CR →Confirmed CR)

CR	Preliminary CR	No	Stable/Better	No	N/A	Confirmed CR
SD	Preliminary PD	No	Stable/Better	Any	Stable/Decreasing	SD (Confirmed PsP)
CR/PR/SD PD/NE	CR/PR/SD/ PD/NE	Yes or No	Worse	Any	Stable/Increasing	Confirmed PD
PD	Preliminary PD	Yes or No	Any	Yes	Stable/Increasing	Confirmed PD

[a] Note that new sites of measurable disease are added to the sum of bidimensional products or total lesion volume, or constitutes preliminary PD in the case of no measurable disease at baseline or best response

For patients with non-enhancing and therefore nonmeasurable tumors, RANO low grade glioma criteria (van den Bent, Lancet Oncology 2011) will be used for response assessment, summarized as follows:

Criterion	CR	PR	MR	SD	PD
T2/FLAIR	Disappearance of all lesions	≥50% ↓ in perpendicular diameters of lesion, sustained for 4 weeks	25–50% ↓ in perpendicular diameters of lesion	<25% ↓ to <25% ↑	≥25% ↑[†]
New lesion	None (apart from those consistent with radiation effects, and no new or increased enhancement)	None (apart from those consistent with radiation effects, and no new or increased enhancement)	None (apart from those consistent with radiation effects, and no new or increased enhancement)	None (apart from those consistent with radiation effects, and no new or increased enhancement)	Present[†]
Corticosteroids	None	Stable or ↓	Stable or ↓	Stable or ↓	NA[‡]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	Stable or ↑	↓[†] (not attributable to other causes apart from the tumor, or decrease in corticosteroid dose)
Requirement for response	All	All	All	All	Any[‡]

[†]Progression occurs when this criterion is met.

[‡]Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

↓: Decrease; ↑: Increase; CR: Complete response; FLAIR: Fluid-attenuated inversion recovery; MR: Minor response; NA: Not applicable; PD: Progressive disease; PR: Partial response; SD: Stable disease.

Unscheduled Assessments:

If an unscheduled assessment is performed and the subject has not progressed, every attempt will be made to perform the subsequent assessments at their scheduled visits (relative to the date of first study drug infusion).

7.6.1. MRI Procedures

MRI of the brain is performed once every 8 weeks on study as per standard of care for the management of recurrent oligodendroglioma. The MRI will be performed on a 3 Tesla scanner. These MRIs do require the use of an FDA-approved gadolinium based contrast agent. The gadolinium will be administered according to the FDA label for gadolinium based contrast.

IV Line Placement – This is required to administer the contrast agent. Multiple needle-sticks may be necessary if a vein cannot be properly accessed and this will be carried out with the subjects' permission.

IV Contrast Risks- As mention above, part of the MRI study will require the injection of a gadolinium contrast agent into the blood stream. There is a rare possibility that the subject could have an adverse reaction to the contrast agent such as rash, hives, itching, mild headache and nausea. The subject may also experience some minor discomfort and low risk of bleeding, infection and bruising associated with Intravenous catheter placement. Most recently, FDA has also required a new class warning for all gadolinium-based contrast agents for MRI concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs. The long-term risks of this retention are not well elucidated. Also, there is a possible risk of nephrogenic systemic fibrosis (NSF, also referred to as nephrogenic fibrosing dermopathy or NFD) occurring following administration of a Gadolinium-based contrast agent in subjects with known moderate to severe renal disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73m2). However, such patients are not eligible for this trial (see ***Section 4*; *Eligibility Criteria***). In addition, serial creatinine values will be checked for each subject once monthly throughout the course of the trial. If at any point a subject's GFR falls below 30 mL/min/1.73m2 or a rise in creatinine above baseline suggests an acute kidney injury, that subject must undergo a repeat serum creatinine test within 24 hours prior to the next planned MRI scan with contrast. This MRI with contrast should not be performed until the GFR is above 30 mL/min/1.73m2 and is stable improving on two additional tests each separated by 48 hours.

Pregnancy Clause - Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. In addition, gadolinium-based IV contrast agents are not approved in pregnant women. However, since there is potential danger to the fetus related to abemaciclib from participating in this protocol for a pregnant woman, pregnant women are already excluded from this study. A negative serum pregnancy test will be required before a woman of child-bearing potential can participate in this study (pregnant women will be excluded from this trial).

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7.7 Safety Assessments

Subjects are evaluated for safety according to the office visit and laboratory evaluation schedule outlined in **Tables 6 and 7** (***Section 6***). In addition, during Cycle 1 of abemaciclib, a phone call to each subject to monitor study drug use at home to ensure over- or under dosing is not occurring (**Table 6; *Section 6*).** Safety and AE definitions, recording, and reporting are outlined in detail in ***Section 9***.

7.8 Tissue and Blood collection for correlative analyses

All enrolled subjects will be asked to provide informed consent to utilize a previously collected formalin-fixed, paraffin-embedded (FFPE) preserved component of archival tumor tissue from the subject's most recent surgical tumor resection for exploratory correlative analyses. This surgery will have already been performed prior to their enrollment on this protocol as part of standard of care therapy for oligodendroglioma. In addition, subjects will be asked to consent to collection of an FFPE preserved component of tumor tissue from any surgical brain tumor resection or brain tumor biopsy that is performed (as clinically indicated) after the subject has discontinued the abemaciclib study drug. Such surgeries are not mandated as part of this protocol.

In addition, 60 mL of peripheral blood will also be collected for plasma cfDNA studies and for other future exploratory correlative analyses. These 60 mL blood samples will be collected at 3 time points per ***Table 6 (Section 6)***: prior to start of abemaciclib, at the start of Cycle 2, and at the EOT visit.

The exploratory endpoints of this study are outlined in *Section 3***.** No results of tissue or blood correlatives will be recorded in the subject's electronic medical record and will not be used in any way to guide treatment or clinical decision making.

7.9 Allowance of Remote Study Activities

During the COVID-19 pandemic, through an IRB approved COVID-19 memorandum exception, certain elements of this study were conducted remotely for patients who were unable to safely travel to Penn Medicine. This allowed us, the study team, to optimize processes for this protocol and therefore conduct many study activities safely and thoroughly without requiring the patient to physically be present at Penn Medicine. Although as of the August 2021 (v6.0) version of this protocol the pandemic conditions are improving, key aspects of this study will continue to be performed remotely for patients who do not live an appropriate driving distance from Philadelphia.

For all subjects, consent, screening and cycle 1 day 1 visits must be completed in person at Penn). However, subsequent lab and MRI assessments may be performed locally, in conjunction with telemedicine provider visits. Additional details are as follows:

> **Alternative distribution of study drug –** Study drug may be shipped directly to the subject. The quantity to be shipped must be reviewed and approved in advance by the Investigator (or designee). Secure, trackable delivery methods (delivery service companies [eg, UPS], and couriers) must be used. Investigator approval is required before each shipment.

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Returning unused study drug, empty study drug packaging, and relevant drug diary pages – For subjects that are scheduled for Day 1 visits via telehealth, the subject will receive a priority overnight shipping label to mail blister packs back to the study team. The completed pill diaries that accompany each cycle may be emailed or faxed to the study team, and/or shipped back with the blister packs. Additionally, return of unused study drug and empty study drug packaging may be delayed until the subject's next visit to the study site.

Telemedicine visits for assessments – Telemedicine visits, preferably via BlueJeans, are permissible for all assessments that can be completed via this mode (eg, medical history, concomitant medications, review of AEs).

Use of laboratories and health-care providers not specified in the clinical trial documentation – For assessments that cannot be completed via telemedicine, the use of health-care providers and laboratories that are not specified in the clinical trial documentation (eg, an imaging facility, clinic, or local practice that is more readily accessible by the subject) is permissible for all assessments that can be completed via this mode (eg, blood collection for laboratory assessments, vitals, ECG, physical examinations, imaging). The Investigator must document their review all of the results provided by laboratories and health-care providers not specified in the clinical trial documentation.

Home health study support − For assessments that cannot be completed via telemedicine, home health-care provider visits are permissible for all assessments that can be completed via this mode (eg, physical examination, collection of laboratory samples). The Investigator must document their review of the results of home health-care provider visits.

Reconsent (ie, consenting to an amended version of the protocol) - Reconsent may be completed virtually and documented in the relevant subject medical records. Investigator must be present during a virtual telemedicine visit to explain the changes, risks and benefits of the study.

8 STATISTICAL PLAN

8.1 Definition of Primary Endpoint

- The primary endpoint of the study is the progression-free survival status of the subject at 6 months after enrollment (PFS-6), either a) tumor progression (as measured by modified RANO criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors) or death due to disease or toxicity; OR b) alive without tumor progression, i.e., a binary endpoint.

8.2 Statistical Methods

8.2.1 Primary Endpoint Analysis (Efficacy of Regimen)

The total sample size for this trial is 10 subjects. A single-stage design is used. The alternative hypothesis of this study is that the proportion of subjects without an event (progression of disease or death due to disease or toxicity) at 6 months from the time of study enrollment will be 85% or higher. We will test this hypothesis against a null hypothesis of 50% of subjects without an event at 6 months. This null hypothesis is based on the historical PFS-6 rate in previous trials

of systemic therapies for oligodendroglioma that has recurred after radiation and alkylating chemotherapy (Chinot et al, *J Clin Oncol* 2001; Triebels et al, *Neurology* 2004; Chamberlain et al, *Cancer* 2009). A PFS-based primary endpoint has been chosen, rather than a response rate primary endpoint, due to both i) the predominantly cytostatic nature of abemaciclic (Klein, *Cancer Cell* 2018), and ii) the fact that a therapy that results in prolonged stable disease, even in the absence of tumor shrinkage, would be of great value in recurrent oligodendroglioma.

With 10 subjects, the power to detect the difference between the null hypothesis of PFS-6 of 50% and the alternative hypothesis of PFS-6 of 85% is 82%, with a probability of type I error (alpha) of 0.10 (one-sided). The study will be considered positive if 8 or greater out of 10 subjects are 6-months event-free.

A subject must have received at least one dose of abemaciclib and have undergone at least one MRI scan after starting abemaciclib in order to be evaluable for the primary endpoint analysis (unless the subject has discontinued abemaciclib prior to the first MRI scan due to disease progression or unacceptable toxicity).

8.2.2 Analysis of Secondary and Exploratory endpoints

Descriptive analyses will be conducted to summarize subject characteristics and detect potential selection bias as a result of missing data or dropout. Variable distributions will be examined; if needed, appropriate transformations will be performed. Paired t-tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are normally distributed. Wilcoxon signed-rank tests will be used to assess change from pre- to post-treatment for exploratory endpoints that are not normally distributed. Multiple comparison adjustment using false discovery rate (FDR) will be used.

All subjects who sign informed consent will be included in safety analyses and in calculation of the rate of AEs, regardless of whether and how much abemacicilb was received.

Objective radiographic response rate (ORR) will be calculated as the proportion of subjects who experience partial or complete radiographic response to abemaciclib, as defined by modified RANO criteria for enhancing tumors and by RANO low grade glioma criteria for non-enhancing tumors (***Section 7***). Progression-free survival (PFS) and overall survival (OS) will be estimated using the Kaplan-Meier product-limit method, with subjects censored at their last known date alive. Standard error for the Kaplan-Meier estimate will be calculated according to the formula of Peto, et al (Br J Cancer 1977) and a two-sided 95% confidence interval for the median OS will also be calculated.

Due to small sample size, comparisons in ORR, PFS, and OS in (1) subjects with *CIC* gene mutation versus subjects without *CIC* gene mutation and (2) subjects who received one prior line of alkylating chemotherapy versus subjects who received more than one prior line will be exploratory in nature and without formal statistical testing.

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9 SAFETY AND ADVERSE EVENTS

9.1 Definitions

9.1.1. Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study, whether or not considered drug-related. This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for assessing the severity of AEs, as follows:

Table 10.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

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Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy, or require changes in the study drug. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal, or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

A preexisting condition is one that is present at the start of the study. A preexisting condition is recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

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9.1.2 Serious Adverse Events

Serious Adverse Event (SAE):
Adverse events are classified as serious or non-serious. An SAE is any AE that is at least one of the following:

- fatal
- life-threatening
- requires hospitalization or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- is considered to be an important medical event, which are those that may not be immediately life threatening but are clearly of major clinical significance. These may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

9.1.3 Unanticipated Adverse Device Effect (UADE)

UADE:
1) Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan
OR
2) Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The only investigational device in this protocol is the test used to document the presence of 1p/19q codeletion.

9.2 Collection and Recording of Adverse Events and UADEs

Adverse event (AE) collection occurs from initiation of study procedures (i.e., from time of signed informed consent form) until the end of the study. As long as consent remains in place, AEs are collected according to the study schedule of events even after subjects are discontinued from abemaciclib treatment for any reason.

At screening, any clinically significant abnormality is recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event are recorded and documented as adverse events.

At each contact with the subject, the investigator seeks information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events is recorded immediately in the source document, and also in the appropriate adverse event module of the electronic case report form (eCRF).

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Each AE should be evaluated to determine:

- The severity grade (CTCAE v5.0, Grade 1 to 4).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in *Section 9.1.2*
- per the Principal Investigator and Sponsor, whether the event is definitely related, probably related, possibly related, or unrelated to the study drug

All adverse events occurring during the study period are recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s). In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The study’s principal investigator is ultimately responsible for the recording, and reporting, unanticipated problems related to the research, which occur during the study.

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9.3 Reporting of Adverse Events, Unanticipated Problems, and UADEs

The study period during which adverse events are reported is defined as the period from the initiation of any study procedures to the end of the study.

9.3.1 Follow-up reporting for SAEs and UADEs

When an SAE has not resolved at the time of the initial report and new information arises, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) is submitted to the IRB. The PI and Sponsor are responsible for ensuring that all SAEs are followed until either resolved or stable.

9.3.2 Investigator Reporting: Notifying the Study Sponsor and Lilly

All investigators should report all adverse events (AEs) to the study PI.

The Sponsor will notify Lilly within two (2) business days of Sponsor receiving notification of any serious adverse event, as defined above in ***Section 9.1.2***, experienced by a subject participating in the Study and related to the abemaciclib study drug. SAEs should be reported to Lilly using a CIOMS Form. Sponsor-Investigator further agrees to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug. In addition to the obligations set forth above, Sponsor- Investigator agrees to provide Lilly with a copy of all information Investigator and/or Sponsor submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Sponsor have not otherwise provided Lilly.

9.3.3 Investigator Reporting: Notifying the Penn IRB

An IRB-reportable event is an incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. In general, an incident is determined to be an IRB-reportable event when it is both (1) unexpected in terms of nature, severity or frequency, and (2) related to participation in the research. If the PI/Sponsor determination notes a causal relationship between the event and the investigational drugs without required revisions to the consent form or other study documents and/or the report indicates that the event does not alter the risk profile of the investigational drug, the event should **not** be classified as reportable to the IRB. The IRB requires investigators to submit reports within 10 working days of discovery for events that meet reporting criteria, with the following exceptions:

The following events must be reported to the University of Pennsylvania IRB within 3 days:

1. Withdrawal from marketing for safety concerns of the drug used in the research protocol.
2. Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team
3. Breach of confidentiality

4. Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
5. Premature completion of a study for any reason

The following events must be reported to the University of Pennsylvania IRB within 24 hours:

1. Any SAE
2. Unanticipated problems/unexpected events:

   Any incident, experience, or outcome that meets all of the following criteria is defined as an **unanticipated problem:**

   - Unexpected in nature, severity, or frequency (i.e. not described in protocol or consent form, the drug package insert, the investigators brochure)
   - Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
   - Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

9.4 Pregnancy

Based on findings in animals, abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for abemaciclib. There are no available human data informing the drug-associated risk. Additionally, there are no available data on effects of breastfeeding.

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method.

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 to be collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit.

10 STUDY ADMINISTRATION, DATA HANDLING, AND RECORD KEEPING

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Investigator and Sponsor retain the ability to use all information collected prior to the revocation of subject authorization.

10.2 Data Collection and Management

Data will be managed in Clinical Trial Management Systems (CTMS). Access to the trial project in CTMS is granted by the Penn Office of Clinical Research (OCR) to all persons with the appropriate roles in the study.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, type "N/D". If the item is not applicable to the individual case, type "N/A".

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. The primary source document for this study is the subject's electronic medical record, i.e. EPIC/PennChart. Other examples of source documents: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Each subject will be assigned a unique study ID number (unique for this project) in CTMS
To ensure that strict confidentiality is maintained, password-protected access to the CTMS project and a file linking medical record numbers (MRNs) to study ID number will be granted only to the clinical research coordinators and research nurses/assistants assigned to this study.

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10.3. Records Retention

Records are retained in accordance with all local, national, and regulatory laws. The Investigator must not destroy any records associated with the study without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. All eCRR data entered, as well as computer hardware and software (for accessing the data), will be maintained or made available at the University of Pennsylvania in compliance with applicable record retention regulations. The Sponsor will retain the original eCRF data and audit trail.

11 STUDY MONITORING, AUDITING, and INSPECTING

11.1 Study Monitoring Plan

This study is monitored by the Sponsor according to the monitoring plan.

11.2 Auditing and Inspecting

The investigator permits study-related monitoring, audits, and inspections by the Sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator ensures the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12 ETHICAL CONSIDERATIONS

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to the University of Pennsylvania Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct.

12.1 Risks

The primary risks to subjects enrolled on this protocol include the following:

- That the experimental regimen will be ineffective against oligodendroglioma, thus permitting the tumor to continue to grow
- That a subject could be enrolled inappropriately due to an error in the in vitro diagnostic test used to determine 1p/19q (and hence eligibility) status for this trial
- Adverse events due to gadolinium-based IV contrast used for MRI scans (although this will be performed according to the FDA label for gadolinium-based contrast); see ***Section 7.6.1***
- Study drug related adverse events, which, in the worst case, could lead to permanent toxicity/injury or death. Full information on the rates of adverse reactions expected with abemaciclib and their management is outlined in detail in the ***Investigator's Brochure.***

12.2 Benefits

Although no benefit can be guaranteed to subjects as a result of enrolling on this protocol, there is strong scientific rationale for studying abemaciclib for CIC-mutated oligodendroglioma (see ***Section 1.2; Study Rationale*).** Therefore, there is a reasonable possibility that subjects enrolled on this study will receive therapy that is more efficacious than current standard of care for recurrent oligodendroglioma (the standard of care is additional cytotoxic chemotherapy, which highly toxic and has a response rate close to zero). In addition, even if the study is negative and does not reach its primary endpoint, there is benefit to medical knowledge and society as a whole from the correlative studies that accompany this trial. These studies are designed to improve our understanding of mechanisms of response and resistance to CDK4/6 inhibition in oligodendroglioma.

12.3 Risk Benefit Assessment

There continues to be a significant unmet need for patients with recurrent oligodendroglioma. The potential benefit to subjects in this study is that abemaciclib may be clinically active and would add additional progression-free and/or overall survival time compared to if the subject did not enroll on the trial. The primary risk to subjects is of adverse events occurring related to abemaciclib.

Overall, the current lack of any proven systemic therapy for oligodendroglioma that has recurred after radiation and alkylating chemotherapy, in combination with the relatively high level of safety and tolerability of the agent abemaciclib, the risk benefit assessment for enrolling in this clinical trial is in favor of benefit.

12.4 Informed Consent Process/HIPAA Authorization

Subjects will be recruited from the Radiation Oncology, Neurosurgery, and Medical Oncology practices at the University of Pennsylvania Health Systems. The treating physician will determine if the patient is a potential research candidate and has the capacity to consent. The treating physician will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating physician will contact a qualified member of the research team in the Neurosurgery Clinical Research Division at the University of Pennsylvania and request availability for enrollment. The PI or sub-investigator will continue the consent process. This person will explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study before making her decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which screening procedures will be performed. Subject eligibility will be evaluated based upon the criteria outlined in the protocol. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study PI. All members of the research team will have successfully completed patient oriented research training.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and

the Sponsor. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

13 STUDY FINANCES

13.1 Funding Source

This clinical trial is financed through a grant from Eli Lilly.

13.2 Conflict of Interest

All University of Pennsylvania Investigators follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14 PUBLICATION PLAN

The Sponsor holds the primary responsibility for publication of the results of the study.

15 REFERENCES

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