INdividualized Screening trial of Innovative Glioblastoma Therapy (INSIGhT)

Protocol Version Date: December 4, 2024

Protocol Version No.: Version 11.0

DF/HCC Protocol No.: 16-443

Coordinating Center: Dana-Farber Cancer Institute

Principal Investigator

Patrick Wen, MD
Dana-Farber Cancer Institute
Center for Neuro-Oncology
450 Brookline Ave, DA-2122
Boston, MA 02115-6084
Phone: (617) 632-2166
Fax: (617) 632-4773
Patrick_Wen@dfci.harvard.edu

Biostatistician

Lorenzo Trippa, PhD
Dana-Farber Cancer Institute
Biostatistics & Computational Biology
450 Brookline Ave
Boston, MA 02115-6084
Phone: (617) 582-9133
Fax: N/A
ltrippa@jimmy.harvard.edu

Co-Investigator

Mehdi Touat, MD
Dana-Farber Cancer Institute
Department of Oncologic Pathology
450 Brookline Ave, JF 215
Boston, MA 02115-6084
Phone: (617) 582-8767
Mehdi_Touat@dfci.harvard.edu

Co-Investigator

Keith Ligon, MD, PhD
Department of Pathology
Dana-Farber Cancer Institute
450 Brookline Ave, JFB 215B
Boston, MA 02115-6084
Phone : (617) 632-2357
Fax : (617) 582-8761
Keith_Ligon@dfci.harvard.edu

Co-Investigator

Howard Colman, MD
Huntsman Cancer Institute
1950 Circle of Hope Dr
Salt Lake City, UT 84112
Phone: (801) 587-4042
Fax: (801) 585-4399
Howard.colman@hci.utah.edu

Co-Investigator

David Peereboom, MD
Cleveland Clinic
9500 Euclid Avenue, S73
Cleveland, OH 44195
Phone: (216) 444-6833
Fax: (216) 444-0924
peerebd@ccf.org

Co-Investigator

Jan Drappatz, MD
University of Pittsburgh Medical Center
5150 Centre Ave, Suite 301
Pittsburgh, PA 15232
Phone: (412) 864-7791
Fax: (412) 623-7862
drappatzj@upmc.edu

Co-Investigator

David Schiff, MD
University of Virginia Health System
1215 Lee Street
Charlottesville, VA 22908
Phone: (434) 924-5610
Fax: (434) 982-6727
Ds4jd@virginia.edu

Co-Investigator

John DeGroot, MD
UT MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 431
Houston, TX 77030
Phone: (713) 745-3072
Fax: (713) 794-4999
jdegroot@mdanderson.org

Co-Investigator

Mary Welch, MD
Columbia University Medical
710 West 168th Street
New York, NY 10032
Phone: (212) 342-0571
Fax: (212) 342-1246
mw2517@cumc.columbia.edu

Co-Investigator

Isabel Arrillaga, MD
Massachusetts General Hospital
55 Fruit Street, Yawkey 9E
Boston, MA 02114
Phone: (617) 724-2887
Fax: (371) 643-2591
iarrillaga@mgh.harvard.edu

Co-Investigator

Eva Galanis, MD
Mayo Clinic
200 1st St SW
Rochester, MN
Phone: (507) 284-2511
Fax: (507) 284-8388
galanis.evanthia@mayo.edu

Co-Investigator

Jaroslaw Hepel, MD
Rhode Island Hospital/Lifespan Comprehensive CancerCenter
593 Eddy Street
Providence, RI 02903
Phone: (401) 444-8311

JHepel@Lifespan.org

Co-Investigator

Thomas Kaley, MD
Memorial Sloan Kettering Cancer Center
1275 York Avenue New York, NY 10065Phone: (212) 639-5122
kaleyt@mskcc.org

Co-Investigator
L. Burt Nabors, MD
University of Alabama at Birmingham
510 20th Street South
Faculty Office Tower 1020
Birmingham, AL 35294
Phone: (205) 934-1432
Fax: 205-975-7546
bnabors@uab.edu

Co-Investigator

Ka-Wai G. Ho MD
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA 02215
Phone: (617) 667-1665
kho5@bidmc.harvard.edu

Responsible Research Nurse: **Lisa Doherty, APRN, BC, OCN**
Dana-Farber Cancer Institute
Lisa_Doherty@dfci.harvard.edu

DFCI Coordinating Center: **Jennifer Wiley**
Research Project Manager
Dana-Farber Cancer Institute
jennifer_wiley1@dfci.harvard.edu

Agents:
Neratinib: Puma Biotechnology
CC-115: Celgene Corp
Abemaciclib: Eli Lilly and Company
QBS10072S: Quadriga Biosciences
VBI-1901: VBI Vaccines
Balstilimab: VBI Vaccines
Temozolomide: commercially available

IND #: 131617
IND Sponsor: Patrick Y. Wen, MD

Funding/Contractual Sponsor: Dana-Farber/Partners Cancer Care, Inc.

Funding Support:
Puma Biotechnology, Inc.
Celgene Corp
Eli Lilly and Company
Quadriga Biosciences
VBI Vaccines
Burroughs Wellcome Fund

SCHEMA

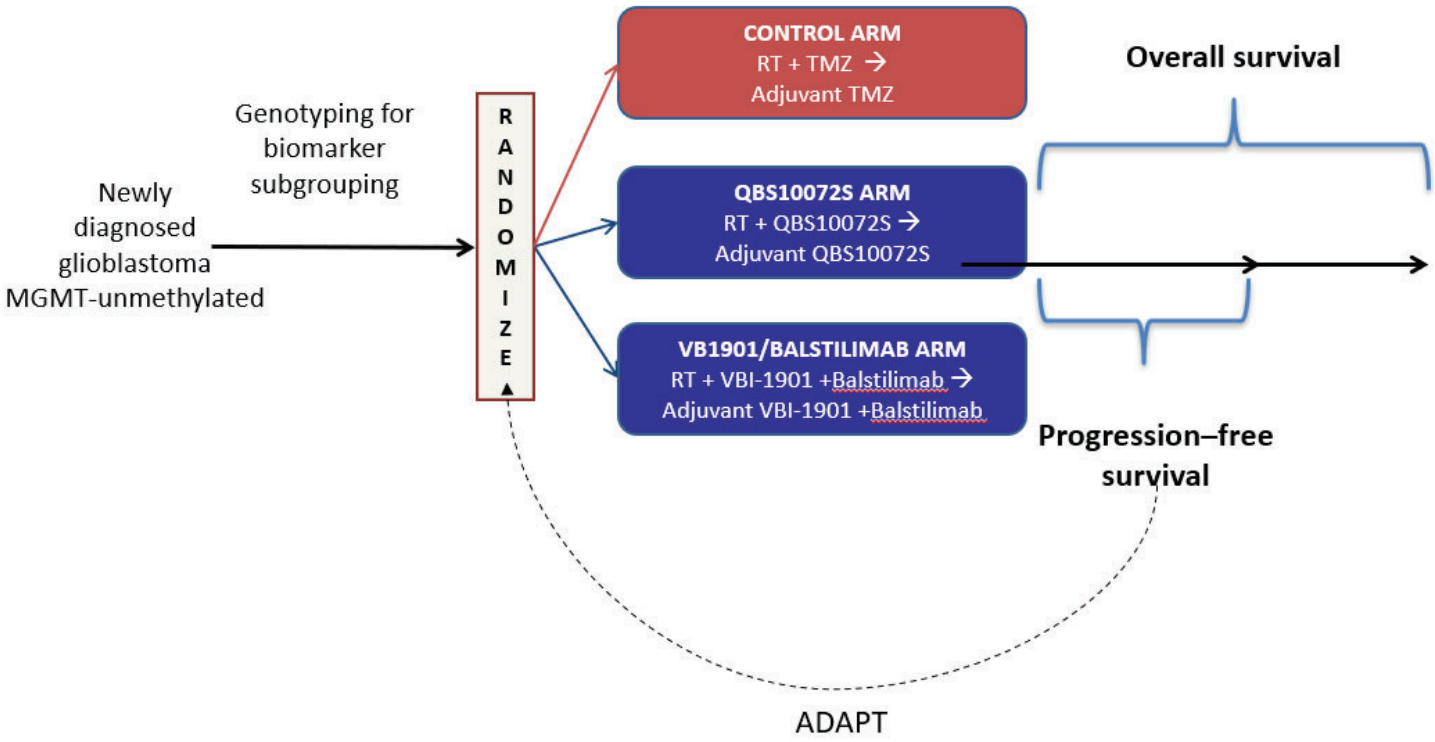

Newly diagnosed glioblastoma MGMT-unmethylated
Genotyping for biomarker subgrouping
RANDOMIZE
CONTROL ARM
RT + TMZ →
Adjuvant TMZ
QBS10072S ARM
RT + QBS10072S →
Adjuvant QBS10072S
VB1901/BALSTILIMAB ARM
RT + VBI-1901 +Balstilimab →
Adjuvant VBI-1901 +Balstilimab
Overall survival
Progression–free survival
ADAPT

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

INSIGhT (INdividualized Screening trial of Innovative Glioblastoma Therapy) is a biomarker-based, Bayesian adaptively randomized, multi-arm phase II platform screening trial designed to test multiple experimental therapy/biomarker hypotheses simultaneously for patients with newly diagnosed glioblastoma (GBM) and unmethylated MGMT promoters.

Patients presenting with newly diagnosed GBM will be enrolled and randomized either to control or one of the experimental arms following surgery, provided that their tumors have unmethylated MGMT promoters, are negative for IDH1 R132H mutation by immunohistochemistry, and have relevant genomic biomarker data either available or in process.

The trial will begin with an initial period of equal randomization among the various arms. Exceptions may occur with arms that need safety lead-ins to determine the safety of the study drug with radiotherapy. Following this initial period, toxicity and efficacy assessments will be made prior to additional randomization. For treatment arms with prior toxicity data, no specific decision-making based on toxicity will be made at this point. For treatment arms designed to give an experimental therapy concurrently with radiation requiring a safety run-in due to known phase II doses, but without prior data in combination with radiation therapy (RT), treatment arms will drop if thereis excess toxicity (as described in Appendix G, Section 3.3). Efficacy assessments, based on progression-free and overall survival compared with control, will be made both for the overall treatment arm and within pre-specified *a priori* genomic biomarker groups for each treatment. This efficacy assessment will be formalized within the adaptive randomization procedure described below, and treatment arms that show evidence of efficacy will preferentially have additional patients randomized to that arm.

1.2 Primary Objectives

- To determine whether experimental arms improve **overall survival** (OS) in patients with GBM harboring unmethylated MGMT promoters compared with standard therapy

1.3 Secondary Objectives

- To determine whether specific *a priori* defined biomarkers predict the benefit from experimental therapy
- To assess the toxicity of experimental arms
- To assess progression-free survival (PFS) among experimental arms and biomarker groups
- To assess OS among experimental arms and biomarker groups
- To determine the association between PFS and OS effects of experimental agents

2. BACKGROUND

2.1 Study Disease

There were an estimated 22,810 cases of primary malignant brain tumors in 2014 of which glioblastoma (GBM) is the most common type[2]. GBM accounts for 45% of primary malignant brain tumors with an average age adjusted incidence rate of 3.19/100,00 during the period of 2006-2010[1]. The prognosis for patients diagnosed with GBM is poor, with 1- and 5-year survival rates were only 35.0% and 4.7%, respectively.

The standard of care for treatment of newly diagnosed GBM patients is based on the results of the landmark European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) trial CE.3 study[2]. This phase III trial randomized 573 patients to concomitant and adjuvant TMZ and RT versus RT alone in patients with newly-diagnosed GBM following surgical resection and showed that the combination of TMZ with RT was well-tolerated and resulted in improved survival (median 14.6 months versus 12.1 months; $p<0.0001$). Methylation of the promoter of the 0^6-methylguanine-DNA-methyltransferase (MGMT) DNA-repair gene in this trial was an independent favorable prognostic factor[3]. Furthermore, many in the neuro-oncology community have interpreted the MGMT results to suggest that there is very limited, if any, benefit from the addition of TMZ to radiation for patients with unmethylated MGMT promoters. As such, this population has been identified for clinical trials which omit TMZ, at least in experimental arms.

2.2 IND Agent(s)

Refer to section 1 of each sub-study appendix for background information on applicable investigational agents.

2.3 Other Agent: Temozolomide

Refer to section 1.1 of applicable sub-study appendices for background information on temozolomide.

2.4 Rationale

Currently, the development of drugs for newly-diagnosed glioblastoma is extremely slow and inefficient. The need for randomized phase II studies with adequate control arms results in half the patient population receiving standard therapy, a significant waste of limited resources and an unattractive situation for patients who have poor outcomes. In addition, the current practice of combining all drugs with radiation therapy and temozolomide (TMZ), even in MGMT unmethylated tumors where the benefit of temozolomide is negligible,[2,4] frequently results in an additional two years of development as the recommended phase II does of the novel agent with radiation therapy and temozolomide is determined. Frequently, dose reduction of the novel agent is required because of overlapping toxicities with TMZ, resulting in an ineffective dose being utilized in the phase II trial with radiation therapy. This trial attempts to overcome some of these limitations and provide and more rapid and efficient framework for developing novel agents for

patients with newly diagnosed glioblastoma with unmethylated MGMT promoters.

The overall rationale for this trial is to rapidly and efficiently screen therapies for impact on overall survival so that they can move on to confirmatory studies for registration purposes. The protocol framework employs an **approach to provide efficient use of a single control arm with multiple experimental arms**. The study will incorporate **high-dimensional genomic data both for pre-specified predictive biomarker hypotheses testing** and for biomarker hypothesis generation. The incorporation of biomarker data has the potential to make clinical trials more efficient by selecting only those populations that are more likely to respond, especially when the biomarker subgroup comprises a minority of the population and the relative effect in biomarker negative vs. positive is strong. **Our approach is initially agnostic to biomarker subgroup-specific effects for randomizing patients to treatment arms but will utilize biomarker data that accumulates during the course of the study that supports biomarker-specific effects.**

The **primary endpoint will be overall survival.** The randomization will be equal randomization to the treatment arms stratified by the biomarker/genomic signature status. Patient data hypothesized to be correlated with overall survival, elements such as progression status and neurocognitive metrics, and performance status, would be included in a model to estimate risk of death. As effects on PFS have been shown to translate to effects on OS for non anti-angiogenic agents in GBM, PFS will be used to inform the adaptive randomization procedure even though the final comparison will be done based on overall survival. As progression free survival outcome data accumulates during the course of the trial, randomization probabilities will be updated to preferentially assign patients to arms that show evidence of improved outcomes based on their biomarker status.
Experimental arms will either **complete accrual or be dropped if the probability of a positive recommendation of confirmatory testing for a single arm falls below 10%.** Futility and efficacy decisions will only be based on evidence directly generated from OS. **New arms will be <u>added through amendment of the protocol once an arm is graduated or dropped, and these experimental arms will be selected by the trial steering committee.</u>** This experimental arm vetting process will consider: strength of the proposed rationale for use in GBM, preclinical/clinical data supporting combination with radiation, preclinical/clinical data supporting specific biomarker subgroup effects, blood-brain barrier penetration, tumor tissue penetration, drug potency, efficacy in standard GBM cell lines both *in vitro* and *in vivo*, efficacy in human tumor derived cell lines both *in vitro* and *in vivo,* prior clinical data, and human safety data either as monotherapy or in combination with radiation therapy. Potential experimental arms will be evaluated and prioritized based on these data, while recognizing that the standard of care is inadequate therapy for these patients, and final recommendations for additional arms will be made by the INSIGhT steering committee. Once the committee has approved an additional arm, the trial documents will be amended accordingly. Individual investigators will be encouraged to take ownership over specific experimental arm additions and will be responsible for assembling the experimental arm proposal and for any publications related specifically related to that arm.

Another major consideration for this trial and any clinical trial for newly diagnosed GBM patients with unmethylated MGMT promoters is how temozolomide (TMZ) should be

considered. The foundation for our decision-making on this issue is that TMZ may have a real but marginal benefit for these patients but that the addition of TMZ has an opportunity cost as well. Whether TMZ has any benefit in the unmethylated setting is certainly debatable, with the most compelling argument being that the benefit seen in the EORTC/NCIC study in unmethylated patients[4] may have been more related to issues assaying true MGMT status or with histopathologic diagnostic errors. Even if this argument is accepted, we do not have a more valid mechanism for assaying MGMT status than in that trial as it relates to the predictive capability of determining who will derive any benefit from the addition of TMZ to RT so we must accept that there may be a small, marginal benefit in these unmethylated patients using our current biomarker technology. For the opportunity cost, there are two major factors to consider. The first is the potential for under dosing an experimental therapy that may have been an improvement over TMZ (whether alone or in combination with RT) at optimal dose due to combined toxicity with TMZ. Some examples of this are phase I trials of BKM120, hydroxychloroquine, and vandetanib in combination with radiation therapy. The second issue is one of time- delaying the entire drug development timeline so that phase I testing in combination with TMZ (which isn't generally done prior to being introduced to a GBM population) can be performed. Informal polling of neuro-oncologists, radiation oncologists, and neurosurgeons from around the country also made it clear that omitting TMZ from clinical trials in an unmethylated population would be acceptable, an opinion reflected in the EORTC experience[4]. Considering these issues, a compromise solution adopted in the current clinical trial design is to keep TMZ as part of the regimen in places where an experimental therapeutic is absent. For example, if there is no radiosensitization hypothesis (as in the arms using neratinib and abemaciclib), TMZ will still be given concurrently with RT but replaced by the experimental therapy in the adjuvant phase. If there is a potential for radiosensitization in addition to single agent activity (CC-115 arm), then TMZ will be omitted altogether.

2.5 Correlative Studies Background

From a diagnostic and treatment perspective, GBM is no longer considered one homogeneous disease. Advances in genetic, epigenetic, gene expression, metabolomic, and other profiling technologies have rapidly been applied to GBM to classify the disease into several different molecularly defined subtypes[5-11]. Such grouping may have direct relevance towards diagnostics, prognosis, and the application of targeted therapy. Currently, MGMT promoter methylation and IDH1 mutation status are routinely used as prognostic[12-14] or predictive[15-16] biomarkers in GBM with some success. Therapeutics directed at precise molecular targets logically lead to hypothetical interactions with alterations in tumor signaling pathways based on the available models or 'wiring diagrams.' The Cancer Genome Atlas identified three major signaling pathways that had recurrent and mutually exclusive genomic alterations, suggesting critical roles for each: receptor tyrosine kinase (RTK)/Ras/phosphatidylinositol-3-kinase (PI3K), p53, and Rb (Figure 1)[8].

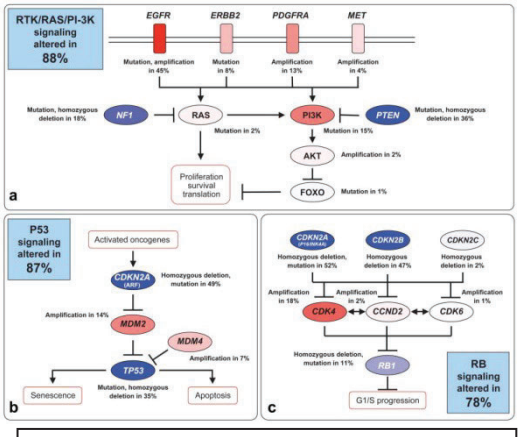


Figure 1: Common genomic alterations in GBM

Genomic analyses and tools are generally less complex and more reliable as biomarkers than RNA based assays and routine genomic analysis is increasingly used in clinical practice and is becoming progressively broader as sequencing costs decrease. Despite the success in other cancers, translating promising targeted therapies for biomarker-identified subgroups into efficacious clinical trials has had little success for GBM to date. Even so, there are many investigational agents that hypothetically interact with the frequently altered pathways listed above which are currently slated for clinical testing. The focus of the current trial is to provide a clinical trial framework to efficiently test these therapeutic hypotheses, both therapeutic efficacy and the predictive capability of the putative biomarker. For this reason, a comprehensive multiplexed genomic analysis will be conducted for each patient to identify biomarker signatures prior to treatment assignment. These biomarker signatures will be evaluated during the course of the trial for association with efficacy signals. Initial biomarker classifiers will be based on 4 specific pathway markers- EGFR amplification/mutation(45%), PI3K activation (PTEN loss through homozygous deletion or mutation plus deletion, PIK3CA mutation, PIK3R1 mutation)(49%), p53 status (MDM 2/4 amplification or p53 wild-type)(65%), and CDK (CDK4/6 amplification or CDKN2A nullisomy)(68%). Genotyping assays or combinations of assays that are able to assign biomarker categories based on these predetermined criteria will be acceptable for inclusion as outlined in Section 9.1.

Initially, patients would be randomized equally to the various treatment arms, regardless of biomarker signature, as there are no strong clinical data supporting the predictive capacity of a genomic biomarker for any of the initial experimental arms. During the course of the trial, the *a priori* biomarker hypotheses will be continuously evaluated for associations with drug efficacy and after the initial predetermined equal randomization period (so not as to be overly influenced by early and limited results) this accumulating clinical data would influence the randomization probability for future enrolled patients should an association be found. For example, if there is an efficacy signal for an EGFR inhibitor, but that signal is limited to the EGFR + group, EGFR – patients would be less likely assigned to the EGFR treatment arm vs. control or drop out altogether while EGFR + would continue to be assigned to EGFR treatment vs. control. In this manner, the initial agnostic randomization will start to utilize biomarker data if it is associated with a treatment effect. For new arms where there are no biomarker signatures randomization based on genomic biomarkers will be omitted.

While a focused panel for these specific genomic aberrations is a possibility, one of the unique aspects of the proposed trial is to acknowledge the lack of well-developed biomarker information in GBM so broader based, multiplexed platforms are encouraged to allow for unbiased discovery/testing of other focused hypotheses about response modifiers based on planned co-clinical trials, in response to other emerging pre clinical or clinical data, or through exploratory discovery analyses.

3. PARTICIPANT SELECTION

Participants must meet all eligibility criteria below prior to initial registration to master INSIGhT protocol. Participants' INSIGhT randomization assignment will be received by the treating study team once the initial registration is processed. See section 4 registration procedures and section 10 screening/registration study calendar for details.

Before beginning study treatment, a second registration confirmation to the assigned treatment arm must be received by the treating team. See section 2 of each sub-study appendix for details on registration procedure to assigned arm.

3.1 Eligibility: Inclusion Criteria

3.1.1 Participants must have histologically confirmed intracranial glioblastoma or gliosarcoma following maximum surgical resection. Tumors primarily localized in the infratentorial compartment will be excluded.

3.1.1.1 Participants with histology of astrocytoma with molecular alterations/features indicative of glioblastoma (WHO grade IV) will be eligible.

3.1.2 Participants may have had prior surgery for glioblastoma or gliosarcoma but no systemic therapy, interstitial chemotherapy (e.g., Gliadel wafers), or radiation therapy. Participants must be recovered from the effects of surgery.

3.1.3 Age ≥ 18 years.

3.1.4 Karnofsky performance status ≥60 (refer to Appendix A).

3.1.5 Participants must have normal organ and marrow function as defined below:

– Leukocytes	≥3,000/µL (≥3 x 10^9/L)
– Absolute neutrophil count	≥1,500/µL (≥1.5 x 10^9/L)
– Platelets	≥100,000/µL (≥100 x 10^9/L)
– Hemoglobin	≥ 9g/dl
– Total bilirubin	Within normal institutional limits (except forparticipants with Gilbert's disease)
– AST(SGOT)/ALT(SGPT)	≤ 2.5 × institutional upper limit of normal
– Creatinine	≤ institutional upper limit of normal OR
– Creatinine clearance	≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.
– Potassium	Within normal institutional range, or correctable withsupplements
– Serum amylase	≤ 1.5 x institutional upper limit of normal
– Serum lipase	≤ 1.5 x institutional upper limit of normal
– INR	< 2.0
– PTT	≤ institutional upper limit of normal, unless receiving therapeutic low molecular weight heparin

3.1.6 Must be able to swallow pills.

3.1.7 Corticosteroid (dexamethasone or equivalent) dosage ≤ 2 mg daily that has been stable or decreasing for at least 5 days

3.1.8 Participants must plan to begin radiation therapy 14-42 days after surgical resection.

NOTE: Patients may be allowed to begin radiation therapy > 42 days after surgical resection provided documented approval is obtained by Dr. Wen - the study's Overall PI - PROSPECTIVELY.

3.1.9 Immunohistochemically negative for IDH1 R132H mutation.

3.1.10 Evidence that the tumor MGMT promoter is unmethylated by standard of care assays.

3.1.11 Genotyping data must be available or in process. 14 USS + 1 H&E will be collected. Confirmation of tissue availability is required for eligibility, but slides can be collected at a later date. NOTE: Patients who do not have sufficient tissue, or when obtaining the requested samples requires depletion of a patient's FFPE block(s), may be eligible provided there is documentation of inadequate tissue AND documented approval is obtained by Dr. Wen - the study's Overall PI - PROSPECTIVELY. All efforts should be made to obtain the maximum number of slides possible, even when prospective approval is granted.

3.1.12 MRI with gadolinium should be obtained within 21 days prior to beginning treatment. Patients without measurable disease are eligible. Participants must be able to undergo MRIs (CTs are not allowed for response assessment on study).

3.1.13 The effects of the experimental agents used in this study on the developing human fetus are unknown. For this reason and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential (women who are not free from menses for > 2 years, post hysterectomy/oophorectomy, or surgically sterilized) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation unless otherwise specified in sub-study appendix that the participant is randomized to. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.14 For women of child-bearing potential (women who are not free from menses for > 2 years, post hysterectomy/oophorectomy, or surgically sterilized) a negative serum pregnancy test must be documented prior to initial registration. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from date of initial dose and for 6 months following the last dose of study drug. Men (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in sexual activity with a woman of child-bearing potential from date of initial dose and for 6 months following the last dose of study drug.

3.1.15 Ability to understand and the willingness to sign a written informed consent document.

3.2 Eligibility: Exclusion Criteria

3.2.1 Participants will not be eligible if the original diagnosis was a lower grade glioma and a subsequent histologic diagnosis revealed glioblastoma.

3.2.2 Planned major surgery.

3.2.3 Participants who are receiving any other investigational agents.

3.2.4 Participants who have had any prior cranial radiotherapy.

3.2.5 History of a different malignancy, unless (a) have been disease-free for at least 2 years and are deemed by the investigator to be at low risk for recurrence of that malignancy, and/or (b) malignancy was cervical cancer in situ, superficial bladder cancer or basal cell or squamous cell carcinoma of the skin, and malignancy has been treated. Patients who meet the above listed criteria and are only on preventative treatment will be deemed eligible.

3.2.6 History of intratumoral or peritumoral hemorrhage if deemed significant by the treating physician.

3.2.7 Impaired cardiac function or clinically significant cardiac diseases, including any of the following:

- 3.2.7.1 Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstableangina, myocardial infarction within 12 months of enrollment, or ventricular arrhythmia.
- 3.2.7.2 Known history of congenital QT prolongation or Torsade de pointes (TdP).
- 3.2.7.3 Complete left bundle branch or bifascicular block.
- 3.2.7.4 QTc interval > 450 ms for men or > 470 ms for women.
- 3.2.7.5 History of clinically meaningful ventricular arrhythmias or atrial fibrillation.
- 3.2.7.6 Unstable pectoris or myocardial infarction ≤ 3 months prior to starting study treatment.
- 3.2.7.7 Uncontrolled hypertension (blood pressure ≥ 160/95 mmHg).
- 3.2.7.8 Other clinically significant heart disease such as congestive heart failure requiring treatment.

3.2.8 Uncontrolled diabetes mellitus, or subjects with either of the following:

- 3.2.8.1 Blood glucose ≥ 200mg/dL (7.0 mmol/L), or
- 3.2.8.2 HbA1c ≥ 8%

NOTE: HbA1c is not a required screening lab; however, if HbA1C is performed at screening, result must be <8%.

NOTE: If patient's HbA1c is ≥ 8%, Team may proceed to register patient with documented explanation (e.g. patient has controlled Type 2 diabetes

mellitus, but steroid dose at time of screening labs has elevated result) and documented confirmation from treating MD that they feel patient is safe to proceed.

3.2.9 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, chronic liver disease (e.g., cirrhosis, hepatitis), chronic renal disease, pancreatitis, chronic pulmonary disease, or psychiatric illness/social situations that would limit compliance with study requirements. Subjects must be free of any clinically relevant disease (other than glioma) that would, in the treating investigator's opinion, interfere with the conduct of the study or study evaluations. Participants with vitiligo, or hypothyroidism due to autoimmune condition only requiring hormone replacement therapy, psoriasis not requiring systemic therapy, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.10 Known immunosuppressive disease or active systemic autoimmune disease such as systemic lupus erythematosus, human immunodeficiency virus infection. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNS [qualitative] is detected).

3.2.11 Known acute or chronic pancreatitis.

3.2.12 Participants with active diarrhea ≥ CTCAE grade 2 despite medical management.

3.2.13 Active infection requiring antibiotics.

3.2.14 Pregnant or breastfeeding.

3.2.15 Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive small bowel resection). Participants with unresolved diarrhea ≥ CTCAE grade 2 will be excluded as previously indicated.

3.2.16 History of allergic reactions attributed to compounds of similar chemical or biologic composition to any of the experimental agents or other agents used in study.

3.2.17 Participants taking an enzyme-inducing anti-epileptic drug (EIAED): phenobarbital, phenytoin, fosphenytoin, primidone, carbamazepine, oxcarbazepine, eslicarbazepine, rufinamide, and felbamate. Participant must be off any EIAEDs for at least 7 days prior to planned start of study investigational agent, excluding Temodar. A list of EIAED and other inducers of CYP3A4 is provided in Appendix C. Among non-EIAED, caution is recommended with use of valproic acid due to potential for drug interaction.

3.2.18 Participants taking a drug known to be strong inhibitors or inducers of isoenzyme CYP3A (Appendix C). Participant must be off CYP3A inhibitors and inducers for at least 7 days prior to planned start of study treatment. NOTE: participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to planned start of study treatment and during the entire study treatment period due to potential CYP3A4 interaction.

3.2.19 Current use of herbal preparations/medications, including but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Participants should stop using these herbal medications

7 days prior to planned start of study treatment.

3.2.20 Current use of warfarin sodium or any other coumadin-derivative anticoagulant. Participant must be off Coumadin-derivative anticoagulants for at least 7 days prior to planned start of study treatment. Low molecular weight heparin and factor Xa inhibitors are allowed.

3.2.21 Participants who may have experienced prior immune-mediated adverse events (e.g., life-threatening pneumonitis).

3.3 Inclusion of Women and Minorities

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

4. INITIAL INSIGHT REGISTRATION PROCEDURES

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration as described in this section below in order to receive INSIGhT randomization assignment.

Before beginning study treatment, a second registration confirmation to the assigned treatment arm must be received by the treating team. See section 2 of each sub-study appendix for details on registration procedure to assigned arm.

Following initial registration, any additional laboratory assessments prior to start of treatment will not be used to re-confirm eligibility. Refer to section 4 of this each sub-study appendix for toxicity management between registration and start of study treatment. Participants should not begin study treatment if a dose hold is required.

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. An initial and second registration must occur prior to the initiation of protocol therapy. Any participant not registered to both the master protocol and assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following initial registration, participants' INSIGhT randomization assignment will be received by the treating study team.

Following second registration (see section 2 of each sub-study appendix for details on registration procedure to assigned arm), participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore®as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. A list of the required forms for registration can be found in Appendix B.

Following second registration to assigned arm, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following second registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

Refer to Appendix B, Section 3.7 for registration details.

5. TREATMENT PLAN

Refer to section 3 of each sub-study appendix for treatment plan details of assigned treatment arm.

5.1 General Concomitant Medication and Supportive Care Guidelines

Refer to section 3 of each sub-study appendix for general concomitant medication and supportive care guidelines of assigned treatment arm.

5.2 Criteria for Taking a Participant Off Protocol Therapy

Refer to section 3 of each sub-study appendix for off-treatment details of assigned treatment arm.

5.3 Duration of Follow Up

Refer to section 3 of each sub-study appendix for duration of follow-up details of assigned treatment arm.

5.4 Criteria for Taking a Participant Off Study

Refer to section 3 of each sub-study appendix for off-study details of assigned treatment arm.

6. DOSING DELAYS/DOSE MODIFICATIONS

Refer to section 4 of each sub-study appendix for dosing delays/dose modification information of assigned treatment arm.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Refer to section 5 of each sub-study appendix for adverse event list and reporting requirements of assigned treatment arm to the corresponding manufacturer and Overall PI/DFCI Coordinating Center.

Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as the study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence or protocol treatment arm, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. When sending reports to the FDA, the Overall PI will clearly indicate what arm of INSIGhT the participant was randomized to.

8. PHARMACEUTICAL INFORMATION

Refer to section 6 of each sub-study appendix for applicable pharmaceutical information of assigned treatment arm.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

Patients eligible for treatment assignment on this study will have had prior genotyping performed under DF/HCC protocol #16-114 (or an alternative platform pre-approved by the Overall PI) including whole genome copy number analysis and whole exome sequencing or another comparable set of genotyping assays that are sufficient to define the biomarker categories below. We will set *a priori* biomarker categories on the basis of genetic aberrations for subsequent analyses:

For amplifications listed, the genotyping report must state clear gene amplification and not gain, which is typically greater than a log2 ratio of +2.0. Copy number losses would be values of less than -0.3 and more than single copy deletions are inferred relative to baseline for the chromosome on which they are located (e.g. single copy Chr 9 loss with additional loss of CDKN2A/B below this level in focal region). The general criteria to be included for mutations would be single nucleotide variants (SNV) that are present at >3% allelic fractions; and have > 5prior events reported in COSMIC or are well established hotspots known to be activating or inactivating mutations through experimental data. All genotyping data will be centrally reviewed by a neuropathologist for ultimate determination of biomarker categories.
It is important to note that biomarker groups were defined on the basis of hypothetical interactions with available therapeutics for study rather than hypothetical functional equivalence. Available supportive preclinical evidence is included below. Given that there is no prior clinical evidence to support a specific biomarker hypothesis and that the preclinical data is limited in some cases, we will learn about biomarker linkages primarily through the conduct of the trial. For that reason, randomization will initially be equal, without regard to biomarker subgrouping or prioritization but biomarker categories will be assessed in the statistical model as outlined in that section.

Assays specifically approved for use on INSIGhT

OncoCopy

aCGH is performed using the Agilent SurePrint G3 1x1M stock chip, which allows analysis of ~

1 million features per sample. Associated reagents include Genomic DNA ULS Labeling Kit (# 5190-0419) and the Agilent Oligo aCGH Hybridization Kit (# 5188-5220). Processed chips are scanned using the Agilent G2565 Series Microarray Scanner (capacity 48 chips per run). The process for analyzing genomic DNA isolated from FFPE materials was initially developed at DFCI[19] and the technique was validated according to ACMG practice guidelines for clinical implementation at the BWH CAMD. ~ 1,000 primary brain tumors specimens have since been analyzed for clinical testing through the Cytogenetics Lab.

Primary brain tumors will be submitted for analysis after review by the neuropathology team at BWH. Samples will have been fixed using standard formalin fixation. Neuropathologists select the most appropriate portions of FFPE blocks to submit for array analysis. FFPE materials received in CAMD are processed for DNA isolation by the Molecular Diagnostics component of CAMD using routine and standard protocols. The degree of DNA fragmentation is estimated by gel electrophoresis[17] and the reference DNA is heat-fragmented to match that of the tumor specimen. We have demonstrated that this size matching is critical to improving the signal to noise ratio in the final aCGH analysis of FFPE specimens. aCGH is then performed using standard protocols.

The data collected for aCGH analysis should be considered semi-quantitative and ordered categorical. The genomic imbalances (losses or gains) reported from each analysis are either present or absent (hence, the data are categorical). The degree to which these imbalances are present or absent in a given tumor can vary (i.e., is one copy of a gene missing or are two copies of a gene missing, or do the data suggest that in a proportion of the tumor two copies, one copy or no copies of the gene are missing --- hence, the data are ordered). The absence or presence of a particular gene or chromosomal locus is called relative to a normal reference genome, and also assumes a diploid genome in the tumor. A combination of biological criteria and limitations of the assay prevent the data from being interpreted in a purely quantitative manner.

Whole exome sequencing

The CRSP Whole Exome Sequencing test takes, as an input, matched tumor and normal specimens from a single patient. Input materials for tumor can be genomic DNA, FFPE tissue, or frozen tissue. For normal sample we will accept whole blood, FFPE (slides or cores), fresh frozen tissue or buffy coats. CRSP performs a sample qualification assay on all samples that are going to be processed through next generation sequencing. Samples are genotyped using a panel of 94 highly polymorphic coding SNPs and a gender specific SNP on the Fluidigm platform. These genotypes, which serve as a genetic fingerprint for each sample, are stored in the sample-tracking database and referenced by our production sequencing pipeline to compare with data from production processes. This “fingerprint” allows immediate confirmation of sample identity. Sample preparation and sequencing: Positive and negative controls are added to matrix plates containing samples. All fluid handling steps are automated on Agilent Bravo liquid handling robots that scan and record receptacle and plate barcodes. Next-generation sequencing libraries are created with custom oligonucleotide adapter molecules incorporating Broad’s validated set of 96 x 96 dual indices for sample multiplexing. Indexed libraries are pooled prior to hybridization of target DNA probes. Selected regions of the genome are pulled down and amplified. Final libraries are quantitated by qPCR and loaded across the appropriate number of Illumina HiSeq 2500 flowcell lanes to achieve the target coverage. Each sample will be sequenced to a mean

target coverage of 200X. Data processing and variant calling: Data from sequencing instruments will be processed through the Broad's established and widely adopted pipelines. Read alignment and duplicate marking will be performed with the Picard analysis suite. Somatic SNV and Indel variants will be called using the latest validated release of the Firehose tools – MuTect[18] and Indelocator.

Primary brain tumors will be submitted for analysis after review by the neuropathology team at BWH. Samples will have been fixed using standard formalin fixation and neuropathologist-reviewed to select areas of >50% tumor and adequacy for molecular analysis. Tumor enriched areas will be macrodissected from 5-10 five-micron sections (FFPE). Genomic DNA will be isolated using standard extraction methods (Qiagen, Valencia, CA) and quantified using Picogreen-based dsDNA detection (Life Technologies, Carlsbad, CA). Samples yielding between 50 and 200ng of DNA will be further processed.

The data collected for whole exome analysis should be considered semi-quantitative and ordered categorical. The genomic imbalances (losses or gains) reported from each analysis are either present or absent (hence, the data are categorical). The degree to which these imbalances are present or absent in a given tumor can vary (i.e., is one copy of a gene missing or are two copies of a gene missing, or do the data suggest that in a proportion of the tumor two copies, one copy or no copies of the gene are missing --- hence, the data are ordered). The absence or presence of a particular gene or chromosomal locus is called relative to a normal reference genome, and also assumes a diploid genome in the tumor. A combination of biological criteria and limitations of the assay prevent the data from being interpreted in a purely quantitative manner.

Other institutional or commercial genotyping assays may be accepted if biomarker categories are able to be determined. More specifically, genotyping assays that are eligible must be performed in a CLIA laboratory setting and assess the entire gene (approximating data from whole exome NGS) for the critical genes included in biomarker groupings described above and approach similar coverage (~ 100x average read depth) as the assays described above. For copy number analysis assays must have log2 ratio copy number data to quantitatively assess relative copy number gains/losses. For example, the assay must readily be able to distinguish single vs. greater than single copy number changes.

If new arms do not have biomarker signatures genomic studies will still be performed but biomarker data will not be used for randomization.

9.2 Exploratory Correlative analysis to evaluate copy number alteration biomarker profiles as predictors of response in the INSIGhT clinical trial

In collaboration with Dr. Orly Alter PhD at the University of Utah, we will correlate clinical trial outcomes data (e.g. progression free survival, overall survival) with novel copy-number signatures and other genomic and clinical parameters to identify predictors of patient response related to standard of care arm or experimental agents studied within the INSIGhT clinical trial.

To perform this additional exploratory, analysis clinical outcomes and other data will be shared and transferred between DFCI and Dr. Alter at University of Utah. All data will be shared in a

de-identified manner. Analysis will be performed and summarized data provided back to the collaborating investigators for integration with other parameters.

Data sharing

Data generated by the INSIGhT clinical trial will be shared publicly once studies are completed and results are approved for sharing by the study PI (Dr. Wen). Data planned to be shared will be de-identified clinical outcomes data and attached genomics data or copy number signature data. De-identified data is planned to be shared at public repositories for purposes of cancer research (e.g. NCI dbGAP, cBioPortal).

10. SCREENING AND REGISTRATION STUDY CALENDAR

The below study calendar should be utilized for purposes of screening and initial registration to master INSIGhT protocol (see section 3 of master protocol for comprehensive eligibility requirements). Refer to section 7 study calendar of each sub-study appendix for additional on-study Day 1 assessments of assigned treatment arm.

NOTE: this table is not comprehensive of assessments required for Day 1 of on-study treatment for each arm.

Assessment	Screening[a]	Registration/ Randomization[b]	On-Study Treatment[c]
Initial Informed Consent[d]	X		
Medical History[e]	X		
Inclusion/Exclusion Criteria[f]	X		
Vital signs[g]	X		
Physical Exam	X		
Neurologic Exam	X		
Karnofsky Performance Status[h]	X		
Concomitant Medications[i]	X		
Pregnancy Test (β-HCG)[j]	X		
Coagulation[k]	X		
Hematology[l]	X		
Serum Chemistry[m]	X		
EKG	X		
Imaging – MRI[n]	X		
Archival Tumor Tissue[t]	X		
Initial Registration[o]		X	
INSIGhT Randomization Assignment[p]		X	
Assigned Arm Informed Consent[q]		X	
Registration to Assigned Arm[r]		X	
Radiation + Assigned Arm Treatment[s]			X[c]

a. Screening: all screening procedures to be performed within 28 days of initial registration unless otherwise specified.
b. Registration/Randomization: initial registration to the master INSIGhT protocol and second registration to subsequent assigned arm must occur prior to beginning study treatment.
c. On-Study Treatment: study treatment may not begin until study team has received second registration confirmation and must begin no later than 42 days from participant's surgical resection. **Refer to section 7 study calendar of each sub-study appendix for additional on-study Day 1 assessments of specific treatment arms. NOTE: this table is not comprehensive of assessments required for Day 1 of on-study treatment.**
d. Initial Information Consent: must be obtained by MD attending. No study specific screening procedures outside of assessments considered standard of care may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration.
e. Medical History: to include review of treatment history for GBM, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
f. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant has met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements.
g. Vital Signs: weight, heart rate, blood pressure, respiration rate, temperature, and height.

h. Karnofsky Performance Status (KPS): see appendix A of master protocol.
i. Concomitant Medications: concomitant medications and reason for administration should be documented from date of consent up to the 30-Day Post Drug Visit.
j. Pregnancy Test: required for women of child bearing potential (please see master protocol section 3 for definition of women of child bearing potential). Pregnancy test can be either blood or urine sample.
k. Coagulation: PT/INR, PT, PTT.
l. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
m. Serum Chemistry: albumin, alkaline phosphatase (ALP), bicarbonate (HCO_3), BUN, calcium, chloride, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, amylase, lipase, magnesium, blood glucose, total protein, total bilirubin (if total bilirubin is greater thanthe upper limit of normal, direct and indirect bilirubin should be performed).
n. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site, Appendix D Recommended MRI Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial.
o. Initial Registration: participants must be registered to the master INSIGhT protocol once eligibility for master INSIGhT protocol (section 3) has been confirmed. **See section 4 of master protocol for details on initial registration procedure.**
p. INSIGhT Randomization Assignment: a participant's randomization assignment will be received by the treating study team once the initial registration is processed.
q. Assigned Arm Informed Consent: must be obtained by MD attending. Following receipt of initial registration/randomization assignment, participants must sign the consent form specific to the assigned treatment arm prior to initiating study treatment.
r. Registration to Assigned Arm: before beginning study treatment, a second registration confirmation to the assigned treatment arm must be received by the treating study team. **See section 2 of each sub-study appendix for details on registration procedure to assigned treatment arm.**
s. Radiation + Assigned Arm Treatment: study treatment may not begin until study team has received second registration confirmation and must begin no later than 42 days from participant's surgical resection. Refer to section 7 study calendar of each sub-study appendix for additional on-study Day 1 assessments of specific treatment arms. **NOTE: this table is not comprehensive of assessments required for Day 1 of on-study treatment.**
t. Archival tumor tissue may be sent to Stanford University for assay laboratory tests.

11. MEASUREMENT OF EFFECT

11.1 Disease Assessment Evaluation

Radiologic assessment will be determined by the Response Assessment in Neuro-Oncology Working Group (RANO) Criteria using primarily bidirectional tumor measurements and include consideration of neurological function and corticosteroid use[19]. The RANO Criteria is outlined in detail in section 11.2 below.
Magnetic resonance imaging (MRI) is the most readily available and reproducible method of disease assessment and is required for this study. The largest and most representative lesions should be measured either on axial, coronal or sagittal slices, and chosen to be followed for response evaluation.

The recommended sequences are outlined in detail in Appendix D and should conform as closely as possible to the consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials[20].

11.1.1 Determination of Radiologic Response

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline (most recent MRI prior to beginning investigational agents for applicable arms or temozolomide for control arm) for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised.

The determination of radiographic response after treatment with agents that affect vascular permeability is particularly difficult. In all patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease.

All measurable and non-measurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Radiologic response and progression will be determined by the local site.

11.1.2 Determination of Progression in Newly Diagnosed Glioblastoma

Approximately 10-30% of patients who received radiation therapy with concomitant temozolomide will have transient worsening of their MRI scans due to treatment effects that improve with time[21]. This phenomenon of "pseudoprogression" may potentially occur more frequently with radiosensitizing agents and immunotherapies.

Detailed discussion of pseudoprogression is outlined in section 11.2.2. In general, the goal is to try to keep patients on therapy as long as possible, provided that they are clinically stable.

The RANO criteria suggests that within the first 12 weeks of completion of radiation therapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease. In general, patients who remain clinically stable and are suspected to have pseudoprogression (preferably based on metabolic or vascular imaging) should continue with their current therapy during the first 12 weeks of completion of radiotherapy. More frequent imaging during this period (e.g. monthly MRIs) may be indicated. Patients should only be discontinued from therapy if there is significant clinical progression or strong suspicion of true progression. For a patient to progress during this period their MRI scan should show an increase by ≥25% in the sum of the products of perpendicular diameters compared to the first post-radiotherapy scan. Additional details are provided in section 11.2 below.

11.2 Imaging Response Criteria

Antitumor response will be evaluated by the Response Assessment in Neuro-Oncology (RANO) working group criteria in this study using primarily the product of the maximal cross-sectional enhancing diameters and include consideration of neurological function and corticosteroid use[19].

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

The recommended sequences will be outlined in detail in Appendix D and should conform as closely as possible to the consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials[20].

11.2.1 Antitumor Effect – Definitions

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

Measurable disease:
Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal diameter of 10 mm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip will be considered to be measurable. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed. Patients without measurable disease, such as those who undergo a gross total resection, cannot respond and can only achieve stable disease as their best radiographic outcome.

Non-measurable evaluable disease:
Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 10 mm.

Number of Lesions:
If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. However, given the heterogeneity of high-grade gliomas and the difficulty in measuring some lesions, a maximum of five of the largest lesions may be measured. In general, the largest enlarging lesion(s) should be selected. However, emphasis should also be placed on lesions that allow reproducible repeated measurements.

Definition of Clinical Deterioration:
The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

Definition of Radiographic Response:
Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or after initiation of therapy should be used for determination of progression. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4 or 8-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. Consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease. All measurable and non-measurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

11.2.2 Pseudoprogression

Radiation Effects

The RANO criteria suggest that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease. It is recognized that the proposed histologic criteria have important limitations, but they provide guidance on the type of findings that are suggestive of progressive disease.

However, it should be noted that pseudoprogression can sometimes occur beyond the 12 weeks after completion of radiotherapy and that new lesions can occur within the radiotherapy field.

In general, patients who remain clinically stable and are suspected to have pseudoprogression (preferably based on metabolic or vascular imaging) should continue with their current therapy especially during the first 12 weeks of completion of radiotherapy. Morefrequent imaging during this period (e.g. monthly MRIs) may be indicated. Patients should only be discontinued from therapy if there is significant clinical deterioration or strong suspicion of true progression. For a patient to progress during this period their MRI scan should show an increase by ≥25% in the sum of the products of perpendiculardiameters compared to the first post-radiotherapy scan. New lesions within the radiationfield will be allowed and will not on their own constitute progression.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Table 1. Criteria for Determining First Progression Depending on Time from Initial Radiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of radiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e. > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy. For a patient to progress during this period their MRI scan should show an increase by ≥25% in the sum of the products of perpendicular diameters compared to the first post-radiotherapy scan. New lesions within the radiation field will be allowed and will not constitute progression. Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition ofprogressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.

Progressive disease ≥12 weeks after radiotherapy completion	1. Stable, or increasing doses of corticosteroids. 2. Increase by ≥25% in the sum of the products of perpendicular diametersbetween the first post-radiotherapy scan, or a subsequent scan with smallertumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication orcomorbid conditions is sufficient to declare progression on current treatment. 4. For patients receiving anti-angiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient onstable or increasing doses of corticosteroids compared with baseline scanor best response after initiation of therapy and not be a result of comorbidevents (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Progressive Disease: Assessment Based on Contrast Enhancing Tumor Measurement

Immune-based therapies are expected to be associated with inflammatory changes that may include edema. RANO expanded radiologic criteria to define progressive disease to include the development of "significantly" increased T2 or FLAIR abnormality because such changes can be a major component defining radiographic progression following therapeutic use of VEGF/VEGFR-targeting therapeutics which are known to elicit potent anti-permeability changes that limit contrast uptake. Studies using immunotherapeutic agents will define radiographic progressive disease by assessment of contrast enhancing tumor burden only and will not incorporate assessment of T2 or FLAIR changes as outlined in RANO because:

1) There is no expectation that immunotherapy agents will falsely diminish enhancingtumor burden as has been noted with anti-angiogenic therapies; and
2) Immune-based therapies may be associated with increased edema and associatedT2/FLAIR changes which may inaccurately be interpreted to represent tumor progression (i.e. pseudoprogression).

11.2.3 RANO Response/Progression Categories

Complete response (CR):

All of the following criteria must be met:

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

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

Partial response (PR):

All of the following criteria must be met:

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

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

Progressive disease (PD):

The following criterion must be met:

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

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

b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c) Any new lesion
d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
e) Failure to return for evaluation due to death or deteriorating condition
f) Patients with non-measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip will also be considered to have experienced progression. The transition from a non-measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 × 9 mm lesion [non-measurable] increasing to a 10 × 11 mm lesion

[measurable]). Ideally, the change should be significant (> 5 mm increase in maximal diameter or ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

Note that if there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

Stable disease (SD):

All of the following criteria must be met:

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

Unknown response status:

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

These RANO Response Criteria are summarized in the following table:

Table 2: Summary of the RANO Response Criteria

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

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

11.2.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment (pretreatment baseline is the most recent MRI prior to beginning investigational agents for applicable arms or temozolomide for control arm). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

11.2.5 Evaluation of Best Response

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

11.2.6 Other Effect Measures

Performance Status:

Participants will be graded according to KPS score.

Overall survival time:

From date of first dose to date of death due to any cause.

Progression-free survival time:

From date of first dose to date of progression or death.

Evaluable participants:

Participants included in primary analysis will be intention-to-treat. That is, all randomized patients will be analyzed according to their randomized treatment assignment, whether or not they were actually treated and whether or not they weretreated appropriately.

11.2.7 Central Radiology Review

The central review of neuroimaging (MRI or CT) will be performed at Dana- Farber Cancer Institute on participants from all study arms when requested from the DFCI Coordinating Center on behalf of the Overall PI. All films of all views from pre-registration (including pre-enrollment scans documenting progression prior to study interventions) and subsequent scans (including all on-study and follow-up scans) will be requested for central review. CDs are preferred.

A copy of all scan reports should be attached for inclusion in the submission. Once the Central Review is complete the Reviewing Physician will document the review results. Once the Central Review is complete, the central review results

may be made available to the local PI or treating investigator.

When requested from the DFCI Coordinating Center, please send a copy of all scans to:

Dr. Patrick Wen c/o Kathryn Partridge
Center for Neuro-Oncology
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
ph: 617-582-9314
fax: 617-582-7782
NeuroOnc_Coord@dfci.harvard.edu

A memo must be submitted to the DFCI Coordinating Center each time submissions are made including DFCI study number, participant identifiers and details of what is being submitted.

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

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in section 5 of each sub-study appendix (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

All sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

The schedule for completion and submission of case report forms (paper and electronic) to the ODQ is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with ODQ, as applicable
On Study Form	Within 30 days of registration
Baseline Assessment Form	Within 30 days of registration
Treatment Form	Within 30 days of the last day of the cycle

Adverse Event Report Form	Within 30 days of the last day of the cycle
Response Assessment Form	Within 30 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 30 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 30 days of the protocol defined follow up visit date or call

12.1.3 Endpoint Data Notification & Source Document Submission

All sites should notify the DFCI Coordinating Center of date of progression and date of death as soon as possible (either via monthly teleconferences hosted by the DFCI Coordinating Center, phone or email). Source documents confirming date of progression and date of death should be submitted to the DFCI Coordinating Center within 5 business days of the site learning of the event. Source documents can be sent directly to DFCI Coordinating Center personnel or to NeuroOnc_Coor@dfci.harvard.edu.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

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

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

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

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

13. STATISTICAL CONSIDERATIONS

The design is a randomized, controlled, multi-arm phase II screening trial designed to estimate the efficacy of various experimental arms through comparison with a single control arm based on overall survival. Randomization probabilities will be updated during the course of the study based on accumulating comparative data regarding progression-free survival. The adaptive algorithms developed by INSIGhT investigators has been previously discussed[25,29,30]. Progression-free and overall survival times for simulations were based on prior clinical trial data for patients with GBM and unmethylated MGMT promoters as discussed in the Background section.

The primary endpoint is the overall survival (OS) of the enrolled patients. Additionally, statistical analyses will compare overall survival (OS) for the experimental arms and the control arm using the standard definition of OS. Power computations and the majority of the simulations used to evaluate the operating characteristics of the trial design and secondary analyses use the proportional hazards model both for PFS and OS.

Statistical analyses will classify patients accordingly to their positive or negative status for the following biomarkers: EGFR, PI3K, and CDK. A biomarker group is defined by the subpopulation of patients with identical status for all these three markers.

Patients will be randomized to the clinical trials arms using an adaptive algorithm that will update the randomization probabilities for the various arms by biomarker grouping monthly. The algorithm uses the available information generated by INSIGhT over the course of the study– the individual biomarker groups and individual PFS (possibly censored) of the enrolled patients– to determine the randomization probabilities that will be used to allocate patients for the subsequent month. These randomization probabilities will be allowed to vary across biomarker groups. The goal of the adaptive algorithm is to accelerate and provide a competitive advantage to those experimental arms associated with promising data early during the study. The adaptive algorithm has the scope of translating promising preliminary evidence based on the PFS data for a single experimental arm into unbalanced randomization probabilities.

INSIGhT investigators explored the advantages of adaptive randomization in accelerating the accrual rate on the most promising experimental arms for patients with GBM previously[25,26]. This work demonstrates that adaptation of randomization probabilities has a relevant effect on the trade-off between power and overall sample size. The adaptive algorithm will define randomization probabilities specific to each biomarker subgroup. This will reflect early evidence based only on preliminary data of treatment effects variations across biomarker subgroups.

We use the same definition of the randomization probabilities studied previously[25,26]. In particular,

the randomization probability to each of the experimental arms is proportional to the associated predicted probability of a positive treatment effect on PFS for the biomarker profile of the enrolled patient. This approach has been recently compared to alternative adaptive schemes for multi-arm adaptive trials with potential biomarker-treatment interactions.

13.1 Sample Size, Accrual Rate and Study Duration

INSIGhT will randomize 50- 70 patients to each of the experimental arms. The overall size of the trial is not fixed by design because we include arm-dropping rules for futility and allow for the possibility of arm addition by amendment. As more arms are added to the trial, we may add additional control patients for comparison requirements. Patients that are non-evaluable or withdraw prior to starting treatment may be replaced. The power computations illustrated below are the major justifications of the sample size. We estimate an accrual rate of 7 patients per month based on prior experience. Sensitivity analyses on the trial operating characteristics considered a range of hypothetical accrual rates, from 5 to 14 patients per month. Our power computations assumed the biomarker frequencies based on data that has been generated from prior genomic profiling[31].

The monthly updates of the randomization probabilities are combined with a sequential decision rule that drops experimental arms when there is insufficient preliminary evidence to warrant further investigation of the treatment based on the primary endpoint. We use a standard linear boundary that thresholds p-values to define the decision rule. This simple early stopping rule reduces the average number of patients allocated to an experimental arm without treatment effects to 49.0, while the average sample size is 69.8 (69.0) with a HR of 0.6 (0.7)[32]. We controlled with a sensitivity analysis for variations of the average sample size for arms without treatmenteffects. By varying accrual rate and treatment effects of the remaining arms we obtained averages between 47 and 50 patients.

The choice of the sample size is primarily driven by power computations. We computed the power of detecting treatment effects under hypothetical scenarios using simulations. Importantely, sample size is justified by the power calculations in presence of treatment effects (i) in the overall populations and (ii) lower power (large differences >30%) of detecting treatment effects limited to biomarker subpopulations, as we report.

Power analysis, detection of PFS treatment effects: If any of the experimental arms has a PFS-HR equal to 0.6 (0.7) on the overall population, the power of rejecting the corresponding primary null hypothesis (overall population PFS-HR $\geq$ 1) at completion of the study is 0.9 (0.79). Power remains stable when we consider variations of accrual rates and outcome distributions forthe remaining arms with values in 0.85-0.92. The power of rejecting the same primary null hypothesis decreases to 0.37 when only the smaller stratum of patients - CDK-positive patients - benefit from the treatment. While the power to reject the null in a biomarker subgroup is of coursereduced, the power to detect a significant biomarker/treatment interaction (null hypothesis: no treatment effect in the CDK positive group) in the secondary analyses is higher (0.66). The fixedmaximum number (70) patients per arm maintains the power of detecting a positive treatment effect for a specific experimental arm stable with respect to the presence or absence of treatment effects on the remaining arms.

Power analysis, detection of OS treatment effects: We defined realistic simulation scenarios with comparable PFS and OS treatment effects measured by median increase under treatments. A similar power analysis as for PFS has been repeated for OS. When OS treatment effects are combined by PFS treatment effects the statistical power of rejecting the null hypothesis (OS-HR≥0) is preserved. With OS-HR equal to 0.6 (0.7) on the overall population, the power of rejecting the null hypothesis at completion of the study is 0.89 (0.77).

13.2 Stratification Factors

Outcomes will be evaluated by biomarker subgroupings as above.

13.3 Interim Monitoring Plan

The interim-monitoring plan will be performed in conjunction with the updates of randomization probabilities. The DFCI Coordinating Center will host monthly all-site teleconferences and will reach out to sites approximately monthly forupdates regarding progression events, deaths, and censoring dates. This data will be compiled and sent to the statistician to update randomization probabilities at which time analyses for futility will be performed. Updated randomization tables will then be forwarded to the Office of Data Quality (ODQ) at the DF/HCC.

13.4 Analysis of Primary Endpoints

The statistical plan includes three primary null hypotheses. Each primary null hypothesis assumes the absence of a superior treatment effects on OS across all biomarker subgroups under a single experimental treatment compared to the control. The primary null hypotheses exclude the possibility of a positive treatment effect for any of the biomarker profiles. As motivated in the literature[28], the statistical plan does not include multiplicity correction for testing these three hypotheses. These analyses will generate p-values under the proportional hazards model. The PI and the statisticians of INSIGhT have discussed the use of p-values for the analysis of data generated from adaptive design[25-27]. All the hypotheses' tests bound the probability of type one errors at 5%.

13.5 Analysis of Secondary Endpoints

The secondary analyses will explore treatment effects variations across biomarker subgroups. These secondary analyses will include estimates of biomarker/treatment interaction coefficients under the stratified proportional hazards model and 95% confidence intervals. These secondary analyses will stratify with respect to patients' biomarker groups. Additionally, secondary statistical analyses will compare PFS versus control. Similar to the primary analyses, the secondary analyses will generate three point estimates of the treatment effects, one for each experimental treatment, and 95% confidence intervals.

14. PUBLICATION PLAN

The results should be made public within 24 months of an arm completing accrual or dropping from the study due to futility. The end of the study is the time point at which the last data items

are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

15. REFERENCES

1. Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol.* 2013; 15 Suppl 2:ii1-56.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *The New England journal of medicine.* 2005; 352(10):987-996.
3. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *The New England journal of medicine.* 2005; 352(10):997-1003.
4. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009; 10(5):459-466..
5. Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer cell.* 2010; 17(5):510-522.
6. Verhaak RG, Hoadley KA, Purdom E, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer cell.* 2010; 17(1):98-110.
7. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell.* 2013; 155(2):462-477.
8. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature.* 2008; 455(7216):1061-1068.
9. Phillips HS, Kharbanda S, Chen R, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer cell.* 2006; 9(3):157-173.
10. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science.* 2008; 321(5897):1807-1812.
11. Reitman ZJ, Jin G, Karoly ED, et al. Profiling the effects of isocitrate dehydrogenase 1 and 2 mutations on the cellular metabolome. *Proceedings of the National Academy of Sciences of the United States of America.* 2011; 108(8):3270-3275.
12. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *The New England journal of medicine.* 2005; 352(10):997-1003.
13. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *The New England journal of medicine.* 2005; 352(10):987-996.
14. Alexander BM, Mehta MP. Role of isocitrate dehydrogenase in glioma. *Expert review of neurotherapeutics.* 2011; 11(10):1399-1409.
15. Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol.* 2012; 13(9):916-926.
16. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol.* 2012; 13(7):707-715.

17. Craig JM, Vena N, Ramkissoon S, et al. DNA fragmentation simulation method (FSM) and fragment size matching improve aCGH performance of FFPE tissues. *PLoS One.* 2012; 7(6):e38881.

18. Cibulskis K, Lawrence MS, Carter SL, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. *Nat Biotechnol.* 2013; 31(3):213-219.

19. Wen PY, Macdonald DR, Reardon DA, et al (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol;28(11):1963-72.

20. Ellingson BM, Bendszus M, Boxerman J, et al. Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro Oncol. 2015 Sep;17(9):1188-98.

21. Brandsma D, Stalpers L, Taal W, et al. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol. 2008 May;9(5):453-61.

22. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical cancer research : an official journal of the American Association for Cancer Research 2009;15:7412-20.

23. Pollack IF, Jakacki RI, Butterfield LH, et al. Antigen-Specific Immune Responses and Clinical Outcome After Vaccination With Glioma-Associated Antigen Peptides and Polyinosinic-Polycytidylic Acid Stabilized by Lysine and Carboxymethylcellulose in Children With Newly Diagnosed Malignant Brainstem and NonBrainstem Gliomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014.

24. Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, Ellingson BM, Hashimoto N, Pollack IF, Brandes A, Franceschi E, Herold-Mende C, Nayak L, Panigrahy A, Pope W, Prins R, Sampson JH, Wen PY, Reardon DA. Immunotherapy Response Assessment in Neuro-Oncology (iRANO): A Report of the RANO Working Group. Lancet Oncology (In Press).

25. Trippa L, Lee EQ, Wen PY, et al. Bayesian adaptive randomized trial design for patients with recurrent glioblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012; 30(26):3258-3263.

26. Wason JM, Trippa L. A comparison of Bayesian adaptive randomization and multi-stage designs for multi-arm clinical trials. *Stat Med.* 2014; 33(13):2206-2221.

27. Ventz S, Trippa L. Bayesian designs and the control of frequentist characteristics: a practical solution. *Biometrics.* 2015; 71(1):218-226.

28. Freidlin B, Korn EL, Gray R, Martin A. Multi-arm clinical trials of new agents: some design considerations. *Clin Cancer Res.* 2008; 14(14):4368-4371.

29. Trippa L, Wen PY, Parmigiani G, Berry DA, Alexander BM. Combining progression-free survival and overall survival as a novel composite endpoint for glioblastoma trials. Neuro-oncology. 2015 Jan 7:nou345.

30. Alexander BM, Wen PY, Trippa L, Reardon DA, Yung WK, Parmigiani G, Berry DA. Biomarker-based adaptive trials for patients with glioblastoma—lessons from I-SPY 2. Neuro-oncology. 2013 Aug 1;15(8):972-8.

31. Ramkissoon, Shakti H., et al. "Clinical implementation of integrated whole-genome copy number and mutation profiling for glioblastoma." *Neuro-oncology* (2015): nov015.

32. Alexander, Brian M., et al. "Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A Bayesian Adaptive Platform Trial to Develop Precision Medicines for Patients With Glioblastoma. " *JCO Precision Oncology* (2019): DOI: 10.1200/PO.18.00071.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B DATA SAFETY MONITORING PLAN

DFCI IRB Protocol #: **16-443**

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

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

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

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

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

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

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

DF/HCC Office of Data Quality: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

2.0 GENERAL ROLES AND RESPONSIBILITIES

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

2.1 DF/HCC Sponsor

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

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

2.2 Coordinating Center

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

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

2.3 Participating Institution

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

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

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

related activities.

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

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

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

3.1 Protocol Distribution

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

3.2 Protocol Revisions and Closures

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

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.
- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

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

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

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

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

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

3.5 IRB Re-Approval

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

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

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization

statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

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

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

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

3.7 DF/HCC Multi-Center Protocol Registration Policy

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

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

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

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

- Obtain written informed consent to master INSIGhT screening procedures from the participant prior to the performance of any study related procedures or assessments.
- Complete the master INSIGhT initial registration eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for initial registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist (in accordance with section 3 of master INSIGhT protocol).**
- **Once initial registration to master INSIGhT protocol is processed, participants' INSIGhT randomization assigned will be received by the treating study team.**

- **Obtain written informed consent to assigned sub-study.**
- **Complete the assigned sub-study registration eligibility checklist.**

Treatment may not begin without confirmation from the Coordinating Center that the participant has completed both initial and second registrations.

Randomization can only occur during ODQ's normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

3.7.1 Participant Registration and Randomization at a non-DF/HCC Site

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

1. The participating site's data manager/coordinator/research nurse should contact a DFCI Neuro-Oncology Coordinating Center team member via telephone or email to:
   - Notify regarding the pending registration
   - Confirm the methods of sending documents and communication for registration
   - Communicate desired timeline of the registration (i.e. within the hour, the next day).

   Multi-Center DFCI Neuro-Oncology Designee contact information:E-mail: NeuroOnc_Coor@dfci.harvard.edu
   Telephone: 617-582-7101

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

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

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

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

3.7.2 Initiation of Therapy

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

3.7.3 Eligibility Exceptions

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

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case

number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Protocol Deviations, Exceptions and Violations

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

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

3.9.1 Definitions

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

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

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

3.9.2 Reporting Procedures

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

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

Protocol violations occurring at a Participating Institution will be submitted to that site's own IRB per the IRB's reporting policy. Whether or not a violation needs to be reported to

the local IRB, notification to the Coordinating Center of any violation should occur in a timely manner. If a report is made to the Participating Institution's IRB, the report and determination should also be forwarded to the Coordinating Center in a timely manner.

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

3.10 Safety Assessments and Toxicity Monitoring

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

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

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

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 5 of each sub-study appendix.

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

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

3.10.2 Guidelines for Processing IND Safety Reports

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

3.11 Data Management

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

3.11.1 Data Forms Review

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

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

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

4.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agents is specified in section 6 of each sub-study appendix.

5.0 MONITORING: QUALITY CONTROL

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

5.1 Ongoing Monitoring of Protocol Compliance

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

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion.

Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants , informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Interim monitoring visits will occur on the following schedule:

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

On-Site Monitoring: On-site monitoring will occur on a regular basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled.

Virtual Monitoring: The Coordinating Center will request source documentation from participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

Regular all-sites teleconferences will be hosted on a monthly basis by the Coordinating Center (unless otherwise specified by the Overall PI). During the teleconferences, sites should convey the following information:

- Updates on participants: holds, dose reductions, significant events, how participant is doing, date of progression and date of death when available and if not already communicated to the Coordinating Center
- Protocol status: which version is being used, and the status of any amendments
- Any Reportable Adverse Events or Deviations/violations that have yet to be communicated to the Coordinating Center (informing the sponsor should not wait for the call, and the call does not supplant communicating the events via the regular email methods of communication).
- Review of prospective participants

If sites are not able to have a representative participant, they should email this information to the Coordinating Center. During the teleconferences, the Coordinating Center may discuss any or all of the following information:

- Accrual/enrollment updates
- Pending amendments
- Safety reports circulated or to be circulated
- ODQ-generated numbers and percentage of missing of missing forms, number of open queries with date of oldest open query, and, for participants on treatment, the date of their last study agent form
- Review of new deviations, violations
- Review of recently received expedited adverse events

5.2 Evaluation of Participating Institution Performance

5.2.1 Monitoring Reports

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

5.3 Accrual Monitoring

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

As this is a Phase II study, Participating Institutions accrual requirement of 5 participants per site annually will be implemented.

6.0 AUDITING: QUALITY ASSURANCE

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

6.1 Audit Plan: DF/HCC Sponsored Trials

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

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

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

6.4 Participating Institution Performance

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

6.4.1 Corrective Actions

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

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

See section 3 of each sub-study appendix for details for detailed instructions on concomitant medications, including use in clinically required situations.

Please note that these lists may not be comprehensive.

Table 1: List of CYP3A Inhibitors and CYP3A Inducers

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

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

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

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

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

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

					sildenafil
					tadalafil
					vardenafil
					Others:
					alfentanyl
					aripiprazole
					Boceprevir
					busprione
					carbamazepine
					gleevec
					haloperidol
					pimozide
					quinine
					tamoxifen
					telaprevir
					trazodone
					vincristine

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

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

APPENDIX D RECOMMENDED MRI ACQUISITION PROTOCOL

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

Table: MRI Protocol

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

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

TR [ms] 2100, TI [ms] 1100, Flip angle 10°–15°, Frequency ≥172, Phase ≥172, NEX ≥1, FOV 256 mm, Slice thickness ≤1.5 mm. Gap/spacing 0, Parallel imaging up to 2x

TR [ms] >6000, TE [ms], 100–140, TI [ms] 2000–2500, Flip angle 90°/≥160°, Frequency ≥256, Phase ≥256, NEX ≥1, FOV 240 mm, Slice thickness ≤4 mm, Gap/spacing 0, Parallel imaging up to 2x

TR [ms] >5000, TE [ms] , Flip angle 90°/180°, Frequency ≥128, Phase ≥128, NEX ≥1, FOV 240 mm, Slice thickness ≤4 mm, Gap/spacing 0, Parallel imaging up to 2x, b = 0, 500, 1000 s/mm2 ≥3 directions

TR [ms] >2500, TE [ms], 80–120, Flip angle 90°/≥160°, Frequency ≥256, Phase ≥256, NEX ≥1, FOV 240 mm, Slice thickness ≤4 mm, Gap/spacing 0, Parallel imaging up to 2x. Post-contrast sequence (10) should be obtained within 8 minutes from time of contrast injection.

APPENDIX E CONTROL ARM OF INSIGHT

TABLE OF CONTENTS

1. BACKGROUND

1.1 Temozolomide

Background and preclinical data
Temozolomide is a member of the imidazotetrazine family that is structurally related to the alkylating agent dacarbazine and has shown efficacy against a variety of cancers, including high grade gliomas.

Under physiologic conditions, temozolomide is spontaneously converted to its active metabolite MTIC (5-(3-dimethyl-1-triazenyl)imidazole-4-carboxamide)[1]. The breakdown product of MTIC, methyldiazonium, is an actively alkylating agent that preferentially methylates guanine residues of the DNA molecule, thereby resulting in single and double DNA strand breaks and activation of apoptotic pathways.[2] Temozolomide has linear and reproducible pharmacokinetics with 100% p.o. bioavailability within 2 hours of drug administration and a rapid plasma drug clearance with a plasma half- life of 1.6-1.8 hours.[3]

Because of its lipophilic properties, temozolomide penetrates into the central nervous system (CNS) and was shown to reach acceptable CNS concentrations. In humans, the CSF penetration is estimated to be ~20-30% based on AUC_{plasma}/AUC_{CSF} ratios.[4] In several preclinical rodent and primate models, it was demonstrated to have activity against CNS tumors thereby stimulating interest for investigations in humans.[5-8]

Clinical data
In these preclinical and clinical phase I studies, temozolomide demonstrated antitumor-activity in high-grade gliomas in adults.[3,9] Based on these studies, the maximal tolerated dose (MTD) for humans has been defined as 150-200 mg/m2 per day depending on whether patients have received prior treatment with myelotoxic agensts.[3,10,11] For patients with glioblastoma, the recommended temozolomide doses are 75 mg/m2 during radiation (concomitant phase) and 150-200 mg/m2 for 5 days out of a 28-day cycle for 6 months.[4,12] Temozolomide in general is well tolerated and the most frequent toxicities are mild to moderate myelosuppression (thrombocytopenia and neutropenia) which is predictable and typically resolves spontaneously.

Subsequent phase II studies confirmed the activity of temozolomide against newly diagnosed and recurrent high-grade gliomas[1,13,14] therefore leading to further evaluation of the drug by the European Organization for Research and treatment of Cancer (EORTC) and the National Cancer Institute of Cancada (NCIC) in a landmark phase III study[15]. In this clinical trial the efficacy of radiation with concomitant temozolomide followed by six monthly cycles of temozolomide compared to radiation alone for newly diagnosed glioblastoma was evaluated[15]. The combination of radiation and temozolomide prolonged median progression free survival from 5 to 6.9 months (95% CI 4.2-5.5) and median overall survival from 12.1 to 14.6 months (95% CI 11.2-13.0). Treatment with temozolomide was overall well tolerated with grade 3 or 4 hematoxicity in 16% of study participants.

Based on these results, this concomitant use of temozolomide during radiation followed by monthly maintenance cycles has been widely accepted as the standard of care treatment for

patients with newly diagnosed glioblastoma.

MGMT

The tumor suppressor gene MGMT (O^6-methylguanine-DNA methyltransferase) on chromosome 10q26 encodes a DNA-repair enzyme that removes alkyl groups from the O^6 position of guanine, thereby repairing the lethal DNA-cross links induced by alkylating chemotherapeutic agents such as temozolomide[16]. Glioma cells with diminished MGMT activity are more responsive to the alkylating damage of these agents[17,18]. Epigenetic silencing of the MGMT promoter is present in ~40-68% of high grade gliomas and leads to reduced protein expression and cellular DNA repair activity. MGMT promoter methylation is associated with longer survival in patients with high grade gliomas treated with alkylating agents[19], including temozolomide[20,21] Therefore, MGMT promoter methylation represents a favorable prognostic marker for high grade gliomas which is routinely evaluated in neuropathological practice.

In a retrospective tumor tissue analysis of the patients enrolled in the EORTC/NCIC study, MGMT promoter methylation was confirmed to be a favorable prognostic factor for patients with glioblastoma.[21] It also showed that the therapeutic benefit of temozolomide in addition to radiation was most pronounced in patients whose tumors contained a methylated MGMT promoter. In this patient group, combined chemoradiation compared to radiation alone prolonged progression-free survival from 5.9 (95% CI 5.3-7.7) to 10.3 (95% CI 6.5-14.0) months and median overall survival from 15.3 (95% CI 13.0-20.9) to 21.7 (95% CI 17.4-30.4) months. In contrast, for patients without MGMT promoter methylation the combination of temozolomide plus radiation resulted in an only small survival benefit compared to radiation alone (progression free survival 4.4 vs, 5.3 months, overall survival 11.8 vs. 12.7 months).

Rationale

These data suggest a correlation between MGMT promoter methylation and treatment response to temozolomide. It therefore can be argued that temozolomide is useful only in the MGMT methylated setting. However, based on the small subgroup of study patients from the landmark EORTC-NCIC study whose tumors were MGMT unmethylated and survived more than 2 years (longer than the expected median survival), there seemed to be a survival benefit from combined radiation and temozolomide compared to radiation alone.[22] In addition, because of issues with the reliability of the assay used to assess MGMT status in this EORTC-NCIC study, it has been debated whether these patients were incorrectly classified as MGMT unmethylated. Nevertheless, based on these data, a real albeit marginal benefit from temozolomide even in the unmethylated setting cannot be excluded. Therefore, it continues to be common practice to use the combination of temozolomide and radiation in all patients with newly diagnosed glioblastoma irrespective of MGMT methylation status.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria Specific to the Control Arm

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration (section 4 of master protocol). Once the randomization assignment has been received following initial registration, all participants randomized to the control arm must meet the following criteria prior to participating in the control arm of the study.

2.1.1 Participants must be willing and able to provide written informed consent/assent for the control arm of the INSIGhT trial.

2.2 Second INSIGhT Registration: Registration to Control Arm

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. Registration to the control arm must occur following initial registration to master INSIGhT protocol and receipt of randomization assignment, and prior to the initiation of protocol therapy. Any participant not registered to their protocol specific assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria in section 2.1 of this sub-study appendix and a member of the study team will complete the protocol-specific eligibility checklist.

Following initial registration, any additional laboratory assessments prior to start of treatment will not be used to re-confirm eligibility. Refer to section 4 of this appendix for toxicity management between registration and start of study treatment.

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

2.2.1 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

2.2.2 Registration Process for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. A list of the required forms for registration can be found in Appendix B.

Following registration, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive

protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Refer to Appendix B, Section 3.7 for registration details.

3. TREATMENT PLAN

Participants treated on this study arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix with concomitant temozolomide (75 mg/m^2/day) daily as described in section 3.2, followed by a 28 (+14 days) day break, and followed by six adjuvant 28-day cycles of temozolomide 150-200 mg/m^2/day x 5 days as described in section 3.4.

Temozolomide will be administered on an outpatient basis. The investigator will instruct the participant to take the drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Participants will be instructed to fast at least 1 hour before and 1 hour after temozolomide administration. Prophylaxis with a 5-HT3 antagonist is recommended prior to administration of temozolomide doses and should be administered orally approximately 30 to 60 minutes before temozolomide treatment. Temozolomide should be taken with a glass of water and consumed over as short a time as possible. Participants should swallow the capsules as a whole and not chew them. Additional drug administration instructions, including missed dose policy, are described in section 6.1.8 of this appendix and are included in the participant pill diary (section 11 & section 12 of this appendix).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires a temozolomide dose delay of > 28 days from the previous dose, the participant must be discontinued from treatment completely. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen, MD at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Participants will keep a medication diary (see section 11 & section 12 of this appendix). At the end of each cycle, the diary will be returned and a new one will be given to the participant.

3.1 Definition of Standard Radiation Therapy

The patient must undergo MRI based treatment planning (CT with contrast-based planning only if patient unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a

minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). The margin may be reduced around natural barriers to tumor growth, and also to allow sparing of organs at risk, if necessary. The PTV volume must be treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast-enhancing region is acceptable. Treatment or no treatment of the T2/FLAIR abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 52 calendar days. Maximum dose (defined as a volume greater than 0.03 cc) to critical structures include: 60 Gy to the brainstem, 56 Gy to the optic chiasm, 55 Gy to the optic nerves, and 50 Gy to the retinae.

Participants are permitted to have radiotherapy as described in this section performed at any NCI funded cooperative group site without prospective Overall PI approval. Prospective Overall PI approval, or approval by his designee (other Coordinating Center radiation oncologists), is required for any radiotherapy site that is not an NCI funded cooperative group site. At the discretion of the DFCI Coordinating Center, a radiation plan may be requested to be prospectively approved for a non-NCI site prior to initiating radiotherapy at the site. Any questions regarding permitted sites should be directed to the DFCI Coordinating Center or Overall PI Patrick Y. Wen, MD.

3.2 Concomitant Temozolomide during Radiation Therapy

Treatment on concomitant therapy should begin no later than 6 weeks from surgery. Temozolomide 75 mg/m^2/day will be administered orally on a continuous daily dosing schedule for a maximum of 49 days. Temozolomide will be initiated on Day 1 of radiation therapy, and the last dose will ideally be the last day of radiation; however, temozolomide may be administered for 42 days, or per your site's institutional policy / standard.

The drug will be administered orally approximately 2-3 hours before each session of radiotherapy. During weekends or weekdays without radiotherapy (Saturday and Sunday), the drug should be taken in the morning when possible. The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The daily dose will be rounded to the nearest 5 mg.

No dose reductions are allowed during the concomitant phase of treatment. If a participant experiences a toxicity related to temozolomide during the concomitant phase of treatment, then temozolomide dosing will be interrupted according the rules described in Table 4.2 of this appendix.

3.3 Rest Phase

During the 28 day (+ 14 days) break after completion of radiotherapy, temozolomide will not be administered.

3.4 Adjuvant (Post-Radiation) Temozolomide

Participants will receive up to 6 cycles of adjuvant temozolomide. Temozolomide will be administered orally once per day for 5 consecutive days (Days 1-5) of a 28-day cycle. The starting dose for the first adjuvant cycle will be 150 mg/m^2/day. If the non-hematologic toxicities for Cycle 1 are Grade ≤ 2 (except for alopecia, nausea, vomiting, lymphopenia and constipation), absolute neutrophil count (ANC) is ≥ 1.5 x 109/L, and the platelet count is ≥ 100 x 109/L., then temozolomide dose may be escalated to 200 mg/m^2/day for adjuvant cycle 2 at the discretion of the treating investigator. The dose remains at 200 mg/m^2/day for subsequent cycles as long as a dose reduction is not requires as per Table 4.2. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

The start of the first adjuvant cycle will be scheduled 28 days (+ 14 days) after the last day of radiotherapy. The start of all subsequent cycles (2-6) will be scheduled every 4 weeks (28 days + 7 days) after the first daily dose of temozolomide of the preceding cycle. The dose will be determined using local institutional standard policy. The daily dose will be rounded to the nearest 5 mg.

3.5 General and Concomitant Medication and Supportive Care Guidelines

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

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

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

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

3.5.3 Anti-seizure medications should be used as indicated. Only participants receiving non-EIAEDs are eligible (although protocol does allow for patients to register and initiate treatment with Temodar and radiation therapy while tapering off EIAEDs). If for unavoidable clinical reasons (emergency department visit, severe allergies, toxicities, etc.) a participant's AED is switched to another AED, the following guidelines must be followed if applicable:

- o Participants should be started on another non-EIAED if at all possible.
- o Participants who are inadvertently and temporarily changed to an EIAED

should immediately be changed to an alternative non-EIAED.

- o Participants who need to permanently change anticonvulsant, but who cannot change to another non-EIAED, must be discussed with the Overall PI.

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

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

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

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

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

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

3.5.10 Other anticancer or experimental therapies: with the exception of tumor treating fields (Optune®), no other anticancer therapy of any kind is permitted during the study treatment period. No other drug under investigation may be used concomitantly with the study drug.

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

3.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 6 adjuvant cycles on the control arm or until one of the following criteria applies:

- Disease progression

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

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

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Patrick Y. Wen, MD, at 617-632-2166 or pwen@partners.org.

3.7 Duration of Follow Up

Participants will be followed until death with monthly visits, telephone contact, or medical record review. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Refer to section 7 study calendar within this appendix for follow-up requirements and time points.

3.8 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

An ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

4. DOSING DELAYS/DOSE MODIFICATIONS

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug. If administration of temozolomide must be interrupted because of unacceptable toxicity, drug dosing will be

interrupted or modified according to rules described in Table 4.2 of this appendix.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

Temozolomide dose reductions are allowed only during the adjuvant cycles. No dose reductions are allowed during the concomitant phase of treatment. If a participant experiences a toxicity related to temozolomide during the concomitant phase of treatment, then temozolomide dosing will be interrupted according the rules described in Table 4.2 of this appendix.

4.1 Anticipated Toxicities

In order for an event to be considered expected (known correlation to study drug/treatment) for the purposes of adverse event reporting, the event must be included in this section or be included in the package insert or the informed consent document as a potential risk.

NOTE: For events that are secondary to an event deemed expected with a study agent/modality (e.g. rectal pain or hypokalemia as a result of diarrhea or gait disturbance as a result of edema cerebral), please record as "possibly related to" and "expected with" the agent/modality.

4.1.1 Anticipated Toxicities for Radiation Therapy

A list of adverse events of all grades suspected to be radiation therapy treatment related, organized by CTCAE v4.03 category, includes:

- EAR AND LABYRINTH DISORDERS – external ear inflammation; other: dryness of ear canal; other: hardening of ear canal wax; external ear pain; other: hearing loss
- ENDOCRINE DISORDERS - other: hypophysitis, or hypopituitarism
- EYE DISORDERS – cataract; other: decreased vision
- GASTROINTESTINAL DISORDERS – nausea; vomiting
- GENERAL DISORDERS – fatigue
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – dermatitis radiation; injury other: optic nerve
- INVESTIGATIONS –lymphocyte count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED – treatment related

secondary malignancy
- NERVOUS SYSTEM DISORDERS – headache; seizure; memory impairment; cognitive disturbance; somnolence; dysgeusia; central nervous system necrosis; edema cerebral; other: tumor inflammation**
- PSYCHIATRIC DISORDERS – personality change
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – scalp pain; other: scalp redness; alopecia

4.1.2 **Anticipated Toxicities for Temozolomide**

A list of adverse events of all grades suspected to be temozolomide treatment related, organized by CTCAE v4.03 category, includes:
- BLOOD AND LYMPHATIC SYSTEM DISORDERS – anemia; febrile neutropenia; bone marrow hypocellular
- GASTROINTESTINAL DISORDERS – constipation; nausea; vomiting; diarrhea
- GENERAL DISORDERS – gait disturbance; fatigue
- IMMUNE SYSTEM DISORDERS – allergic reaction
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – bruising; hemorrhage
- INVESTIGATIONS – neutrophil count decreased; lymphocyte count decreased; white blood cell decreased; platelet count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NERVOUS SYSTEM DISORDERS – dizziness; memory impairment; headache; seizure
- PSYCHIATRIC DISORDERS – insomnia
- REPRODUCTIVE SYSTEM AND BREAST DISORDERS – infertility
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – alopecia

* "Generalized muscle weakness" to also include other CTCAE terms inclusive of a muscle weakness

** As CTCAE v. 4 recognizes 'Edema cerebral' only as a Gr4 event, please record events of 'Edema cerebral' deemed by Investigator to be Gr1-Gr3 or Gr5 as 'Nervous system disorders, Other: Tumor inflammation' (Gr1-Gr3 or Gr5, accordingly).

4.2 Dose Modifications/Delays for Temozolomide

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

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

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

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

4.2.3 Participants cannot be treated below dose level -1. If a participant whose temozolomide dose has been reduced to dose level -1 and requires another dose reduction, treatment on study must be stopped unless the participant has benefited from the study, in which case the investigator will contact the overall Principal Investigator, Dr. Patrick Y. Wen, to determine if the participant will remain in the study.

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

4.2.4.1 NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

4.2.5 Dose re-escalation (after dose reduction for toxicity) is never permitted in this study.

4.2.6 Study teams are not required to hold for lymphopenia.

4.2.7 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 4.2 of this appendix, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of temozolomide. All SAEs must be reported as detailed in Section 5.3 of this appendix.

Adjuvant Temozolomide Dose Levels

Dose Level	Dose of Temozolomide ($mg/m^2/day$)	Remarks
1	200	Escalated dose for adjuvant cycle2*
0	150	Starting dose for adjuvant cycle 1
-1	100	

* Dose may be escalated to 200 mg/m^2/day beginning adjuvant cycle 2 at the discretion of the treating investigator if the non-hematologic toxicities for Cycle 1are Grade ≤ 2 (except for alopecia, nausea, vomiting, lymphopenia and constipation), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L.

Table 4.2: Criteria for dose-modification and re-initiation of Temozolomide treatment

For toxicities attributable to temozolomide (considered at least possibly related), Table 4.2 should be adhered to as noted below. When the treating investigator feels that a hold or reduction of temozolomide is warranted for patient safety even though the toxicity is unrelated to temozolomide, discussion with the Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Toxicity (organized per CTCAE v 4.03)	Concomitant Temozolomide	Adjuvant Temozolomide
Neutropenia **- Grade 2 (ANC 1.0 - 1.4 x 109/L)**	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level. If a dose reduction is required < 100 mg/m^2, then discontinue TEMOZOLOMIDE.
Neutropenia **- Grade 3 (ANC 0.5 - 0.9 x 109/L)**	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.	Interrupt until resolution to ≤ grade 1, then resume TEMOZOLOMIDE at one lower dose level. If a dose reduction is required < 100 mg/m^2, then discontinue TEMOZOLOMIDE.
Neutropenia **- Grade 4** **(ANC < 0.5 x 10^9/L)**	Discontinue TEMOZOLOMIDE	Discontinue TEMOZOLOMIDE
Thrombocytopenia **- Platelet count: 50 - 99 x 109/L**	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, then resume TEMOZOLOMIDE at the current dose level.	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, then resume TEMOZOLOMIDE at the current dose level. If a dose reduction is required < 100 mg/m^2, then discontinue TEMOZOLOMIDE.
Thrombocytopenia **- Platelet count: 10 - 49 x 10^9/L**	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, then resume TEMOZOLOMIDE at the current dose level.	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, then resume TEMOZOLOMIDE at one lower dose level. If a dose reduction is required < 100 mg/m^2, then discontinue TEMOZOLOMIDE.

Toxicity (organized per CTCAE v 4.03)	Concomitant Temozolomide	Adjuvant Temozolomide
Thrombocytopenia **- Platelet count: < 10 x 10^9/L**	Discontinue TEMOZOLOMIDE	Discontinue TEMOZOLOMIDE
Non-hematologic toxicity (except for alopecia, nausea, vomiting, constipation, weight loss, & anorexia) **- Grade 2**	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.	Interrupt until resolution to ≤ grade 1, then resume TEMOZOLOMIDE at one lower dose level. If a dose reduction is required < 100 mg/m^2, then discontinue TEMOZOLOMIDE.
Non-hematologic toxicity (except for alopecia, nausea, vomiting, constipation) **- Grade 3**	Discontinue TEMOZOLOMIDE	Interrupt until resolution to ≤ grade 1, then resume TEMOZOLOMIDE at one lower dose level. If a dose reduction is required < 100 mg/m^2, then discontinue TEMOZOLOMIDE.
Non-hematologic toxicity (except for alopecia, nausea, vomiting, constipation) **- Grade 4**	Discontinue TEMOZOLOMIDE	Discontinue TEMOZOLOMIDE

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (section 4.1 of this appendix) and the characteristics of an observed AE (Section 5.2 of this appendix) will determine whether the event requires expedited reporting **in addition** to routine reporting.

This section specifies reporting requirements to the FDA, Overall PI/Coordinating Center, DF/HCC IRB, and manufacturer as applicable.

5.1 Expected Toxicities

Refer to section 4.1 of this appendix for expected toxicities for assigned study treatment arm.

5.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in section 4.1 of this appendix should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

5.3 Expedited Adverse Event Reporting

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

5.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event that is *Serious, Unexpected,* and there is a *Reasonable Possibility* (i.e., possible, probable, or definitive attribution) the Adverse Event is related to the study intervention.

5.3.3 **Expedited Reporting Guidelines to Overall PI/Coordinating Center**

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

External investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. As mentioned in 5.3.2, external investigative sites will reports AEs per table below in accordance with DF/HCC reporting policy. If an event must be reporting per table 5.3.3:

1. Document/describe reportable AE(s) on the following:
   a. MedWatch 3500A
   b. DFCI Reportable AE Coversheet found in section 10 of this appendix
2. Email above documents to NeuroOnc_SAE@dfci.harvard.edu with the subject title "INSIGHT SAE"
   a. All AE reports received at this account are forwarded immediately to Overall Principal Investigator (Dr. Patrick Y. Wen), and to Coordinating Center personnel.

Table 5.3.3 Expedited AE Reporting by external sites to Coordinating Center/Overall PI

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	5 business days#	5 business days	1 business day*
Possible Probable Definite	Not required	5 business days	5 business days#	5 business days	1 business day*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

5.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

- Lymphopenia (grades 2-4)
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for treatment of patient's underlying disease after coming off study treatment (e.g. admission after patient is removed from active study treatment for craniotomy)

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

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

5.5 Expedited Reporting to Hospital Risk Management

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

5.6 Routine Adverse Event Reporting

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

6. PHARMACEUTICAL INFORMATION

Temozolomide

6.1.1 Description

The chemical name of Temozolomide is 3,4-dihydro-3methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide and the molecular weight is 194.15, which acts as an alkylating agent.

In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 1.6 to 1.88 hours. Following oral administration, the drug, Temozolomide, is rapidly absorbed and then hydrolyzed to the active metabolite 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC spontaneously degrades to CO_2 and 5-aminoimidazole-4-carboxamide (AIC) and excreted via the urine. CYP isoenzymes play an only minor role in Temozolomide metabolism.

6.1.2 Form

Temozolomide drug will be supplied commercially.

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of Temozolomide and the inactive ingredients sodium starch glycolate, tartaric acid, stearic acid, and colloidal silicon dioxide.

The body of the capsules is made of gelatin, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength.

6.1.3 Storage and Stability

Temozolomide is stable at room temperature.

6.1.4 Compatibility

There are no known compatibility issues.

6.1.5 Handling

Routine chemotherapy handling is recommended.

6.1.6 Availability

Temozolomide is available through special pharmacy and can be prescribed by the treating physician.

6.1.7 Preparation

None

6.1.8 Administration

- Temozolomide capsules should not be opened or chewed; they must be swallowed whole with a glass of water one hour before or after food and other medications.
- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.
- If the participant forgets to take his/her temozolomide dose more than 10 hours from intended dosing time, then that dose should be withheld and temozolomide should be restarted at the time of the next planned dose.

6.1.9 Ordering

Temozolomide drug will be supplied commercially and should be ordered per local policy.

7. STUDY CALENDAR

Assessment	Screen-ing[a]	Concomitant							Rest[e]	Adjuvant Cycles		End of Tx[h]	30-Day Post Drug[i]	Active Follow-Up[j]	Long Term Follow-Up[k]
		D1[b]	D8[c]	D15[c]	D22[c]	D29[c]	D36[c]	D43-49[d]		D1[f]	D22[g]				
Informed Consent[l]	X														
Medical History[m]	X														
Inclusion/Exclusion Criteria[n]	X														
Vital signs[o]	X	X			X			X		X		X			
Physical Exam	X	X			X			X		X		X			
Neurologic Exam	X	X			X			X		X		X			
Karnofsky Performance Status[p]	X	X			X			X		X		X			
Concomitant Medications[q]	X														
Adverse Events[r]	X														
Pregnancy Test (β-HCG)[s]	X	X			X					X		X			
Coagulation[t]	X														
Hematology[u]	X	X	X	X	X	X	X	X	X[cc]	X	X	X			
Serum Chemistry[v]	X	X			X			X	X[cc]	X		X			
EKG[w]	X														
Radiation[x]		X													
Temozolomide		X								X					
Imaging – MRI[y]	X	X								X		X		X	
Response Assessment[z]										X		X		X	
Post-treatment therapies[aa]														X	X
Survival[bb]														X	X
Archival Tumor Tissue[h]	X														

a. All screening procedures to be performed within 28 days of initial registration unless otherwise noted. **NOTE: refer to section 10 of master protocol for comprehensive details on screening assessments, initial registration, randomization assignment and second registration timing.**

b. Concomitant radiation and temozolomide must begin no later than 42 days following initial surgery. Day 1 assessments must be performed within 3 days of starting study treatment. Screening assessments may be utilized as baseline assessments if they fall within window.

c. +/- 2 day window for weekly assessments during concomitant phase.

d. Day 43-49 visit to occur within +/- 7 days of completing radiation.

e. Rest period is 28-42 days.

f. Adjuvant cycles to begin >28 (+14) days following end of radiation. Subsequent adjuvant cycle to begin >28 (+7) days from day 1 of previous cycle. **Adjuvant cycles can be**

extended > 28 days per protocol when the next cycle's treatment is held. Day 1 adjuvant assessments to be performed within 4 days prior to Day 1 temozolomide.

h. End of Treatment: assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment.
i. 30-Day Post Drug: a contact/visit is to be performed 30 days (+/-7 days) after date of last drug taken on study. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last drug. If the 30-day Post Drug window falls within the End of Treatment time point, a separate contact does not need to be obtained.
j. Active Follow-Up: participants who discontinue study treatment for reasons other than disease progression will be followed every 4 weeks (+/-1 week) via contact or medical record review and study team must continue monitoring participant's disease status by radiologic imaging at 8 week intervals (+/- 1 week) until (1) documented disease progression, (2), death, (3) participant withdraws from follow-up, or (4) end of study, whichever occurs first.
k. Long Term Follow-Up: participants will be followed every 4 weeks (+/-1 week) via contact or medical record review until death. Participants must be followed for survival data at every long-term follow-up time point and for post-treatment therapies and reason for stopping those therapies when available.
l. Informed Consent: must be obtained by MD attending. No study specific screening procedures may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration. Following initial registration and receipt of INSIGhT randomization assignment, participants must be sign the consent form specific to the assigned treatment arm prior to initiating treatment for that study arm.
m. Medical History: to include review of treatment history for GBM, any ongoing medical conditions & medical history pertaining to eligibility on study and involvement during study.
n. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements for initial registration. See section 2 of this appendix for arm specific eligibility criteria.
o. Vital Signs: weight, heart rate, blood pressure, respiration rate, temperature. Vital signs must be performed prior to administration of treatment on treatment days. Height required only at screening.
p. Karnofsky Performance Status (KPS): see appendix A of master protocol.
q. Concomitant Medications: Concomitant medications & reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.
r. Adverse Events: adverse events experienced by participants will be collected and recorded from the first dose of treatment on-study up to the 30-Day Post Drug Visit of the last dose of study medication (+/- 7 days depending on when 30-Day Post Drug visit/contact occurs).
s. Pregnancy Test: required for women of child bearing potential (see section 3 of master protocol for definition of women of child bearing potential).).
t. Coagulation: PT/INR, PT, PTT required at screening only and then as clinically indicated.
u. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
v. Serum Chemistry: albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greaterthan the upper limit of normal, direct and indirect bilirubin should be performed)
w. EKG: required at screening only and then as clinically indicated.
x. Radiation: see section 3.1 of this sub-study appendix for definition of standard radiation therapy per protocol.
y. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site,Appendix D Recommended Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial. Local reading (investigator assessment) will be used to determine eligibility and for participant management. Adjuvant C1D1 imaging should be performed within 7 days prior to starting adjuvant treatment; subsequent imaging should be performed within 7 days prior to Day 1 of odd cycles.
z. Response Assessment: Per RANO criteria (see section 11 of master protocol).
aa. Post-treatment Therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected when available.

bb. Survival: date of death and reason must be collected for overall survival purposes.
cc. Hemes & Serum Chemistries will be done as per SOC during patient's post-RT.
dd. Archival tumor tissue may be sent to Stanford University for assay laboratory tests.

8. MEASUREMENT OF EFFECT

Refer to section 11 of master INSIGhT protocol for details on measurement of effect.

9. REFERENCES

1. O'Reilly SM, Newlands ES, Glaser MG, et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. *Eur J Cancer.* 1993; 29A(7):940-942.
2. Koukourakis GV, Kouloulias V, Zacharias G, et al. Temozolomide with radiation therapy in high grade brain gliomas: pharmaceuticals considerations and efficacy; a review article. *Molecules.* 2009; 14(4):1561-1577.
3. Newlands ES, Blackledge GR, Slack JA, et al. Phase I trial of temozolomide (CCRG 81045: M&B 39831: NSC 362856). *Br J Cancer.* 1992; 65(2):287-291.
4. Ostermann S, Csajka C, Buclin T, et al. Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. *Clin Cancer Res.* 2004; 10(11):3728-3736.
5. Patel M, McCully C, Godwin K, Balis FM. Plasma and cerebrospinal fluid pharmacokinetics of intravenous temozolomide in non-human primates. *J Neurooncol.* 2003; 61(3):203-207.
6. Stevens MF, Hickman JA, Langdon SP, et al. Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-methyl-imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M & B 39831), a novel drug with potential as an alternative to dacarbazine. *Cancer Res.* 1987; 47(22):5846-5852.
7. Friedman HS, Dolan ME, Pegg AE, et al. Activity of temozolomide in the treatment of central nervous system tumor xenografts. *Cancer Res.* 1995; 55(13):2853-2857.
8. Plowman J, Waud WR, Koutsoukos AD, Rubinstein LV, Moore TD, Grever MR. Preclinical antitumor activity of temozolomide in mice: efficacy against human brain tumor xenografts and synergism with 1,3-bis(2-chloroethyl)-1-nitrosourea. *Cancer Res.* 1994; 54(14):3793-3799.
9. Brada M, Judson I, Beale P, et al. Phase I dose-escalation and pharmacokinetic study of temozolomide (SCH 52365) for refractory or relapsing malignancies. *Br J Cancer.* 1999; 81(6):1022-1030.
10. Hammond LA, Eckardt JR, Baker SD, et al. Phase I and pharmacokinetic study of temozolomide on a daily-for-5-days schedule in patients with advanced solid malignancies. *J Clin Oncol.* 1999; 17(8):2604-2613.
11. Dhodapkar M, Rubin J, Reid JM, et al. Phase I trial of temozolomide (NSC 362856) in patients with advanced cancer. *Clin Cancer Res.* 1997; 3(7):1093-1100.
12. Stupp R, Dietrich PY, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol.* 2002; 20(5):1375-1382.
13. Bower M, Newlands ES, Bleehen NM, et al. Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma. *Cancer Chemother Pharmacol.* 1997; 40(6):484-488.

14. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer.* 2000; 83(5):588-593.

15. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005; 352(10):987-996.

16. Kaina B, Christmann M, Naumann S, Roos WP. MGMT: key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents. *DNA Repair (Amst).* 2007; 6(8):1079-1099.

17. Jaeckle KA, Eyre HJ, Townsend JJ, et al. Correlation of tumor O6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with bis-chloroethylnitrosourea: a Southwest Oncology Group study. *J Clin Oncol.* 1998; 16(10):3310-3315.

18. Silber JR, Blank A, Bobola MS, Ghatan S, Kolstoe DD, Berger MS. O6-methylguanine-DNA methyltransferase-deficient phenotype in human gliomas: frequency and time to tumor progression after alkylating agent-based chemotherapy. *Clin Cancer Res.* 1999; 5(4):807-814.

19. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med.* 2000; 343(19):1350-1354.

20. Hegi ME, Diserens AC, Godard S, et al. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res.* 2004; 10(6):1871-1874.

21. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005; 352(10):997-1003.

22. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009; 10(5):459-466.

10. DFCI REPORTABLE AE COVERSHEET – INSIGHT CONTROL ARM

DF/HCC Protocol No. 16-443

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this AE):
☐ Dr. Patrick Y. Wen and Dana-Farber Coordinating Center Email: NeuroOnc_SAE@dfci.harvard.edu

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

Participant # and Initials:	
Date Event Met Reporting Criteria (as defined in protocol):	
Type of Report: ☐Initial ☐Follow-up	Hospitalization? ☐ Yes ☐ No

CTCAE Event #1 Description:	CTCAE Event #2 Description (if applicable): *NOTE: use another coversheet if more than 2 events are being reported at this time*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5
Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected	Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected
Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite	Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite
Expectedness to **Temozolomide**: ☐Expected ☐Unexpected	Expectedness to **Temozolomide**: ☐Expected ☐Unexpected
Attribution to **Temozolomide**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite	Attribution to **Temozolomide**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite
Reporting Investigator (print):	

Signature of Reporting Investigator:_____Date:_____

11. TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

To be completed by study personnel:

Patient ID #_____Patient Initials: _____Month & Year:_____**Temodar Dose:_____mg**

Take_____capsule(s) at_____mg strength +_____capsule(s) at_____mg strength

+_____capsule(s) at_____mg strength

This treatment diary is for you to indicate that you took the study drug as prescribed. **Please bring this treatment diary and your pill bottle(s) with you to each clinic visit. At the end of the cycle, please sign and date the bottom of the treatment diary.**

Temodar Instructions

During radiation therapy, **Temodar** should be taken daily (including weekends and holidays) – your Clinical Team will confirm the total # of days you will take Temodar**.**

- Temodar capsules should be taken whole (do not chew or open capsules), two to three hours prior to radiation with a full glass of water on an empty stomach (one hour before or after food and other medications).
- If you realize you have missed a dose by more than 10 hours, the dose should not be retaken and the next dose should not be increased to make up for the missed dose. Please indicate missed doses on this diary.
- If a dose is vomited, the capsules are not to be replaced and you can indicate this vomited dose on the diary.
- On days when you do not have radiation, Temodar should be taken in the morning on an empty stomach (one hour before or after food and other medications) with a full glass of water.
- If your course of radiation extends beyond 42 days because of delays, the course of Temodar may be extended to a maximum of 49 days.

Please check with your study treatment team if you have any questions regarding how or when you should take your Temodar doses.

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 8	**DAY 9**	**DAY 10**	**DAY 11**	**DAY 12**	**DAY 13**	**DAY 14**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 15	**DAY 16**	**DAY 17**	**DAY 18**	**DAY 19**	**DAY 20**	**DAY 21**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials

Participant/Guardian Signature:_____ **Date:** _____

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 22	DAY 23	DAY 24	DAY 25	DAY 26	DAY 27	DAY 28
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 29	**DAY 30**	**DAY 31**	**DAY 32**	**DAY 33**	**DAY 34**	**DAY 35**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 36	**DAY 37**	**DAY 38**	**DAY 39**	**DAY 40**	**DAY 41**	**DAY 42**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials

Participant/Guardian Signature:_____ Date: _____

To be completed by study personnel: Patient ID #________Patient Initials:________Month & Year:___________Temodar Dose:____________mg

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 43	DAY 44	DAY 45	DAY 46	DAY 47	DAY 48	DAY 49
Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ ____________ Patient Initials

Participant/Guardian Signature:____ **Date:** ____________________

12. TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY FOLLOWING RADIATION THERAPY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Month & Year:_____**Temodar Dose:_____mg**

Take_____capsule(s) at_____mg strength +_____capsule(s) at_____mg strength

+_____capsule(s) at_____mg strength

This treatment diary is for you to indicate that you took the study drug as prescribed. **Please bring this treatment diary and your pill bottle(s) with you to each clinic visit. At the end of the cycle, please sign and date the bottom of the treatment diary.**

Temodar Instructions

- Temodar should be taken daily on days 1-5 of each 28-day cycle**.**
- Temodar capsules should be taken whole (do not chew or open capsules), at approximately the same time each day with a full glass of water on an empty stomach (one hour before or one hour after food).
- If you realize you have missed a dose by more than 10 hours, the dose should not be retaken and the next dose should not be increased to make up for the missed dose. Please indicate missed doses on this diary.
- If a dose is vomited, the capsules are not to be replaced and you can indicate this vomited dose on the diary.

Please check with your study treatment team if you have any questions regarding how or when you should take your Temodar doses.

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY FOLLOWING RADIATION THERAPY

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: OFF Temodar	Date: OFF Temodar
DAY 8	**DAY 9**	**DAY 10**	**DAY 11**	**DAY 12**	**DAY 13**	**DAY 14**
Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar
DAY 15	**DAY 16**	**DAY 17**	**DAY 18**	**DAY 19**	**DAY 20**	**DAY 21**
Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar
DAY 22	**DAY 23**	**DAY 24**	**DAY 25**	**DAY 26**	**DAY 27**	**DAY 28**
Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar	Date: OFF Temodar

Participant/Guardian Signature:_____ Date: _____

APPENDIX F ABEMACICLIB ARM OF INSIGHT

TABLE OF CONTENTS

1. BACKGROUND

1.1 Temozolomide

Background and preclinical data

Temozolomide is a member of the imidazotetrazine family that is structurally related to the alkylating agent dacarbazine and has shown efficacy against a variety of cancers, including high grade gliomas.

Under physiologic conditions, temozolomide is spontaneously converted to its active metabolite MTIC (5-(3-dimethyl-1-triazenyl)imidazole-4-carboxamide)[1]. The breakdown product of MTIC, methyldiazonium, is an actively alkylating agent that preferentially methylates guanine residues of the DNA molecule, thereby resulting in single and double DNA strand breaks and activation of apoptotic pathways.[2] Temozolomide has linear and reproducible pharmacokinetics with 100% p.o. bioavailability within 2 hours of drug administration and a rapid plasma drug clearance with a plasma half- life of 1.6-1.8 hours.[3]

Because of its lipophilic properties, temozolomide penetrates into the central nervous system (CNS) and was shown to reach acceptable CNS concentrations. In humans, the CSF penetration is estimated to be ~20-30% based on AUC_{plasma}/AUC_{CSF} ratios.[4] In several preclinical rodent and primate models, it was demonstrated to have activity against CNS tumors thereby stimulating interest for investigations in humans.[5-8]

Clinical data

In these preclinical and clinical phase I studies, temozolomide demonstrated antitumor-activity in high-grade gliomas in adults.[3,9] Based on these studies, the maximal tolerated dose (MTD) for humans has been defined as 150-200 mg/m2 per day depending on whether patients have received prior treatment with myelotoxic agensts.[3,10,11] For patients with glioblastoma, the recommended temozolomide doses are 75 mg/m2 during radiation (concomitant phase) and 150-200 mg/m2 for 5 days out of a 28-day cycle for 6 months.[4,12] Temozolomide in general is well tolerated and the most frequent toxicities are mild to moderate myelosuppression (thrombocytopenia and neutropenia) which is predictable and typically resolves spontaneously.

Subsequent phase II studies confirmed the activity of temozolomide against newly diagnosed and recurrent high-grade gliomas[1,13,14] therefore leading to further evaluation of the drug by the European Organization for Research and treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) in a landmark phase III study[15]. In this clinical trial the efficacy of radiation with concomitant temozolomide followed by six monthly cycles of temozolomide compared to radiation alone for newly diagnosed glioblastoma was evaluated[15]. The combination of radiation and temozolomide prolonged median progression free survival from 5 to 6.9 months (95% CI 4.2-5.5) and median overall survival from 12.1 to 14.6 months (95% CI 11.2-13.0). Treatment with temozolomide was overall well tolerated with grade 3 or 4 hematoxicity in 16% of study participants.

Based on these results, this concomitant use of temozolomide during radiation followed by maintenance cycles has been widely accepted as the standard of care treatment for

patients with newly diagnosed glioblastoma.

MGMT

The tumor suppressor gene MGMT (O^6-methylguanine-DNA methyltransferase) on chromosome 10q26 encodes a DNA-repair enzyme that removes alkyl groups from the O^6 position of guanine, thereby repairing the lethal DNA-cross links induced by alkylating chemotherapeutic agents such as temozolomide[16]. Glioma cells with diminished MGMT activity are more responsive to the alkylating damage of these agents[17,18]. Epigenetic silencing of the MGMT promoter is present in ~40-68% of high grade gliomas and leads to reduced protein expression and cellular DNA repair activity. MGMT promoter methylation is associated with longer survival in patients with high grade gliomas treated with alkylating agents[19], including temozolomide[20,21] Therefore, MGMT promoter methylation represents a favorable prognostic marker for high grade gliomas which is routinely evaluated in neuropathological practice.

In a retrospective tumor tissue analysis of the patients enrolled in the EORTC/NCIC study, MGMT promoter methylation was confirmed to be a favorable prognostic factor for patients with glioblastoma.[21] It also showed that the therapeutic benefit of temozolomide in addition to radiation was most pronounced in patients whose tumors contained a methylated MGMT promoter. In this patient group, combined chemoradiation compared to radiation alone prolonged progression-free survival from 5.9 (95% CI 5.3-7.7) to 10.3 (95% CI 6.5-14.0) months and median overall survival from 15.3 (95% CI 13.0-20.9) to 21.7 (95% CI 17.4-30.4) months. In contrast, for patients without MGMT promoter methylation the combination of temozolomide plus radiation resulted in an only small survival benefit compared to radiation alone (progression free survival 4.4 vs, 5.3 months, overall survival 11.8 vs. 12.7 months).

Rationale

These data suggest a correlation between MGMT promoter methylation and treatment response to temozolomide. It therefore can be argued that temozolomide is useful only in the MGMT methylated setting. However, based on the small subgroup of study patients from the landmark EORTC-NCIC study whose tumors were MGMT unmethylated and survived more than 2 years (longer than the expected median survival), there seemed to be a survival benefit from combined radiation and temozolomide compared to radiation alone.[22] In addition, because of issues with the reliability of the assay used to assess MGMT status in this EORTC-NCIC study, it has been debated whether these patients were incorrectly classified as MGMT unmethylated. Nevertheless, based on these data, a real albeit marginal benefit from temozolomide even in the unmethylated setting cannot be excluded. Therefore, it continues to be common practice to use the combination of temozolomide and radiation in all patients with newly diagnosed glioblastoma irrespective of MGMT methylation status.

1.2 Abemaciclib (LY2835219)

Rationale & Proposed Biomarker Association

Rb signaling plays an important role in cell growth and division. During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division[23,24]. The CDK4/CyclinD complex regulates the G1 restriction point through phosphorylation of the Rb tumor suppressor protein. With the possible exception of those

tumors with complete inactivation of Rb, which functions downstream of the CDK4/6-cyclinD complex, all these cancers are potentially sensitive to pharmacologic inhibition of CDK4/6.

From a therapeutic standpoint, the goal of inhibiting CDK4/6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth. LY2835219 is a selective and potent small molecule CDK4/6 dual inhibitor that demonstrates significant inhibition of tumor growth in GBM xenograft models with an intact, functional RB1 protein.

Selective inhibition of CDK4/6 results in a reversible arrest of cancer cells at the restriction point when used as a single agent in cells containing functional Rb protein. Other cell biology has confirmed and demonstrated that LY2835219 mesylate inhibits CDK4/6 to induce G1 arrest specifically in Rb-proficient tumors. Orthotopic xenograft experments with primary human GBM cell lines showed that treatment with LY2835219 extended survival in CDK6 amplified and Rb wild type lines.

Preclinical data

Abemaciclib demonstrates significant inhibition of tumor growth in GBM human xenograft models. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 days to 28 days. In preclinical species, abemaciclib demonstrates moderate to high bioavailability, with a terminal elimination half-life ($t_{1/2}$) in plasma ranging from approximately 17 to 38 hours. The radioactivity associated with [14C]LY2835219 distributes well into tissues and organs, with concentrations measurable through 24 hours post-dose in various parts of brain in rat. Abemaciclib therefore distributes extensively to the brain *in vivo* and produces a statistically significant and dose dependent **improvement in survival in a rat orthotopic brain tumor model (Figure 1)**. Median survival was improved 8 and 12 days compared to vehicle following daily oral treatment at 40 mg/kg and 80 mg/kg for 21 days, respectively. Preclinical data demonstrates that abemaciclib inhibits CDK4/6 to induce G1 arrest **specifically in Rb-proficient tumors**.

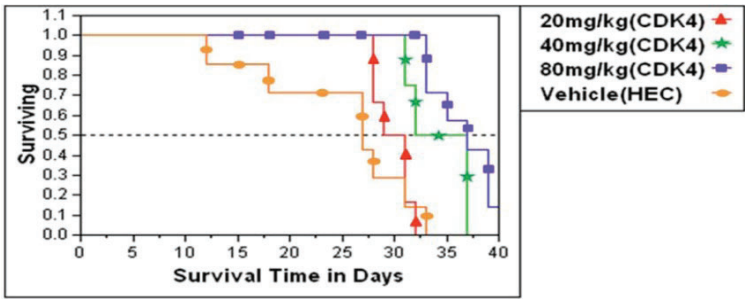


Figure 1: Improvement in overall survival with LY2835219 in rat orthotopic brain model.

In primary human tumor xenograft models, abemaciclib also demonstrates tumor growth delay and a prolongation of survival. Abemaciclib was initiated day 6 post tumor cell injection as oral gavage once daily at either 45 or 90 mg/kg/administration. Normalized bioluminescence was reduced in tumors treated with either dose level, which led to a statistically significant improvement in survival (Figure 2, left two panels) in the GBM43 line, which has wild-type RB. Similar results were shown for GBM39, a primary human tumor line with CDK6 amplification (Figure 2, right two panels).

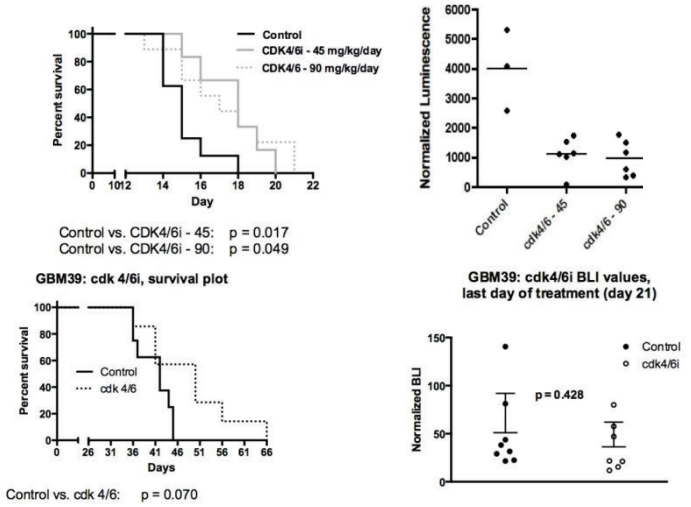


Figure 2: Reduced bioluminescence and improved overall survival in primary human tumor xenograft models with wild-type Rb (left two panels) or CDK6 amplification (right two panels).

Other

CDK4/6 inhibitors have also shown preclinical efficacy in GBM. Palbociclib, a CDK 4/6 inhibitor from Pfizer, extended survival in an intracranial xenograft GBM model (Figure 3). Of note, RT followed by CDK 4/6 inhibition seemed to produce the most favorable survival in comparison to concurrent therapy or inhibition followed by RT. While the palbociclib results were also compelling, abemaciclib was felt to have superior BBB penetration in comparison.

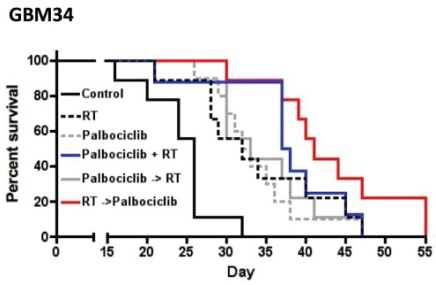


Figure 3: Improved survival for palbociclib following RT in an intracranial xenograft model.

Clinical data

There are 7 studies completed and 13 studies ongoing. Study JPBA is a multicenter, nonrandomized, open-label Phase 1 study of abemaciclib in patients with advanced cancer. In Part A (the dose-escalation phase), patients were treated on 2 different schedules: either at 50, 100, 150, and 225 mg every 24 hours (Q24H), or at 75, 100, 150, 200, and 275 mg every 12 hours (Q12H). In Parts B, C, D, E, and F the tumor-specific expansion phases), patients are treated on the twice-daily schedule at a dose no greater than the MTD with administration of abemaciclib on Days 1 through 28 of a 28-day cycle, The MTD was not reached for the once-daily schedule and for the twice-daily schedule was established at 200 mg Q12H. Based on the frequency of Grade 1/2 diarrhea during an interim analysis and the observation of clinical activity at doses below the below the MTD, the initial starting dose was changed to 150 mg Q12H to gain additional PK data and clinical experience around safety/tolerability. As the diarrhea was found to be managable with standard antidiarrheal agents, early treatment with antidiarrheal agents was recommended and the initial starting dose was returned to 200 mg Q12H. The Phase 2 study, JPBB, is a proof-of-concept trial for patients with mantle cell lymphoma. Abemaciclib is administered orally at 200 mg Q12H on Days 1 through 28 of a 28- day cycle. Study JPBD is an open-label study to determine the disposition of labeled abemaciclibin healthy surgically sterile or postmenopausal females or sterile males following oral administration of a single 150-mg dose of abemaciclib containing approximately 5μCi of [14C]- abemaciclib. No data is available at this time for Study JPBD.

As of 14 October 2015, validated safety data for 572 patients treated with abemaciclib were available in Studies JPBA, JPBB, JPBC, JPBH, JPBJ, and JPBN. The most common TEAEs possibly related to study drug included diarrhea (73.3%), fatigue (48.6%), nausea (48.3%), neutropenia (32.9%), vomiting (25.3%), decreased appetite (25.2%), thrombocytopenia (22.9%), anemia (22.4%), leukopenia (20.3%), abdominal pain (18.2%), and blood creatinine increased (14.0%). As of 14 October 2015, 146 patients in ongoing and completed studies experienced 222 SAEs possibly related to study drug. SAEs that were experienced by more than 5 patients included diarrhea (17 patients), anemia (13 patients), neutropenia (12 patients), dehydration (11 patients), acute kidney injury and nausea (10 patients each), pneumonia (8 patients), pulmonary embolism (7 patients), febrile neutropenia (6 patients), and vomiting (5 patients).

In the tumor expansion cohorts, plasma and CSF was collected for patients with primary brain tumors and metastases. Plasma and CSF concentrations from patients were obtained after reaching steady state with < 2.5 hours between plasma and CSF sampling (Figure 4) and supported the preclinical observations of distribution extensively in the CSF.

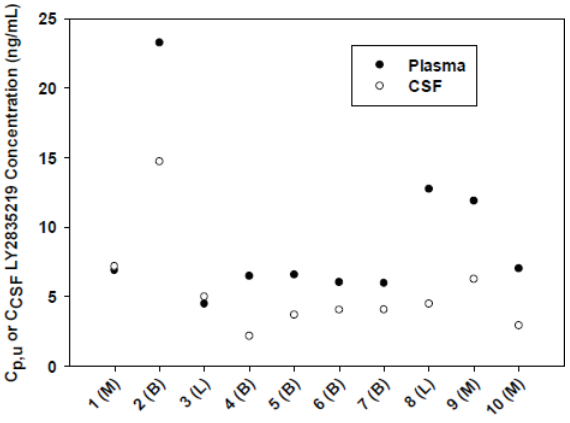


Figure 4: Plasma and CSF concentrations for 10 patients treated with abemaciclib.

Seventeen patients with GBM that had progressed or recurred after radiotherapy and/or chemotherapy enrolled in Part C of Study I3Y-MC-JPBA. Abemaciclib was given as a single agent at a dose of 200 mg orally every 12 hours on Days 1 through 28 of a 28-day cycle. In this progressive/recurrent GBM cohort, the disease control rate **(DCR = response + stable disease) was 17.6% and median PFS was 1.1 months**. It should be noted that 13 of the 17 patients were heavily pretreated patients who had failed bevacizumab. In the 4 heavily pretreated patients who had not received bevacizumab, 2 patients experienced prolonged disease stability (**1 patient has received 19 cycles** and **1 patient received 23 cycles. Both remained on treatment with stable disease at data cutoff**.

There is no compelling data to combine abemaciclib with RT in a radiosensitizing strategy so the experimental arm will maintain TMZ during RT and then abemaciclib will replace TMZ in the adjuvant phase.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria Specific to the Abemaciclib Arm

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration (section 4 of master protocol). Once the randomization assignment has been received following initial registration, all participants randomized to the abemaciclib arm must meet the following criteria prior to participating in the abemaciclib arm of the study.

2.1.1 Participants must be willing and able to provide written informed consent/assent for the abemaciclib arm of the INSIGhT trial.

2.1.2 Women of child bearing potential (women who are not free from menses for > 2 years, post hysterectomy/oopherectomy, or surgically sterile) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from date of intial dose and for 3 months following the last dose of abemaciclib.

2.2 Second INSIGhT Registration: Registration to Abemaciclib Arm

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. Registration to the abemaciclib arm must occur following initial registration to master INSIGhT protocol and receipt of randomization assignment, and prior to the initiation of protocol therapy. Any participant not registered to their protocol specific assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria in section 2.1 of this sub-study appendix and a member of the study team will complete the protocol-specific eligibility checklist.

Following initial registration, any additional laboratory assessments prior to start of treatment will need be used to re-confirm eligibility. Refer to section 4 of this appendix for toxicity

management between registration and start of study treatment.

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

2.2.1 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

2.2.2 Registration Process for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. A list of the required forms for registration can be found in Appendix B.

Following registration, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Refer to Appendix B, Section 3.7 for registration details.

3. TREATMENT PLAN

Participants treated on the abemaciclib arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix with concomitant temozolomide (75 mg/m^2/day) daily as described in section 3.2, followed by a 28 (+14 days) day break, and followed by continuous twice daily dosing of abemaciclib as described in section 3.4 below.

3.1 Definition of Standard Radiation Therapy

The patient must undergo MRI based treatment planning (CT with contrast-based planning only if patient unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). The margin may be reduced around natural barriers to tumor growth, and also to allow sparing of organs at risk, if necessary. The volume must be treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast-enhancing region is acceptable. Treatment or no treatment of the T2/FLAIR abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 52 calendar days. Maximum dose (defined as a volume greater than 0.03 cc) to critical structures include: 60 Gy to the brainstem, 56 Gy to the optic chiasm, 55 Gy to the optic nerves, and 50 Gy to the

Participants are permitted to have radiotherapy as described in this section performed at any NCI funded cooperative group site. Prospective Overall PI approval, or approval by his designee (other Coordinating Center radiation oncologists), is required for any radiotherapy site that is not an NCI funded cooperative group site. At the discretion of the DFCI Coordinating Center, a radiation plan may be requested to be prospectively approved for a non-NCI site prior to initiating radiotherapy at the site. Any questions regarding permitted radiotherapy sites should be directed to the DFCI Coordinating Center or Overall PI Patrick Y. Wen, MD.

3.2 Concomitant Temozolomide during Radiation Therapy

Treatment on concomitant therapy should begin no later than 6 weeks from surgery. Temozolomide 75 mg/m^2/day will be administered orally on a continuous daily dosing schedule for a maximum of 49 days. Temozolomide will be initiated on Day 1 of radiation therapy, and the last dose will ideally be the last day of radiation; however, temozolomide may be administered for 42 days, or per your site's institutional policy / standard.

The drug will be administered orally approximately 2-3 hours before each session of radiotherapy. During weekends or weekdays without radiotherapy (Saturday and Sunday), the drug should be taken in the morning when possible. The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The daily dose will be rounded to the nearest 5 mg.

No dose reductions are allowed during the concomitant phase of treatment. If a participant experiences a toxicity related to temozolomide during the concomitant phase of treatment, then temozolomide dosing will be interrupted according the rules described in Table 4.2 of this appendix.

Temozolomide will be administered on an outpatient basis. The investigator will instruct the participant to take the drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Participants will be instructed to fast at least 1 hour before and 1 hour after temozolomide administration. Prophylaxis with a 5-HT3 antagonist is recommended prior to administration of temozolomide doses and should be administered orally approximately 30 to 60 minutes before temozolomide treatment. Temozolomide should be taken with a glass of water and consumed over as short a time as possible. Participants should swallow the tablets as a whole and not chew them. Additional drug administration instructions, including missed dose policy, are described in section 6.1.8 of this appendix and are included in the participant pill diary (section 11 of this appendix).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires a temozolomide dose delay of > 28 days from the previous dose, the participant must be discontinued from further temozolomide treatment. If a participant discontinues temozolomide due to toxicity, the participant may continue study treatment with adjuvant cycles of abemaciclib as described in section 3.4 below. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen, MD at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Participants will keep a temozolomide diary (see section 11 of this appendix). After completion of radiation, the diary will be returned.

3.3 Rest Phase

During the 28 day (+ 14 days) break after completion of radiotherapy, temozolomide will not be administered.

3.4 Adjuvant (Post-Radiation) Abemaciclib

Adjuvant cycles of abemaciclib should begin no sooner than 28 days (+ 14 days) following the completion of radiation therapy. Participants cannot begin adjuvant abemaciclib if they meet any criteria requiring a dose modification as outlined in section 4.3 of this appendix. All adjuvant cycle 1, day 1 assessments (as noted in section 7 study calendar of this appendix) must be resulted and reviewed prior to initiating treatment with abemaciclib.

The study drug, abemaciclib, will be administered on an outpatient basis. The investigator will instruct the participant to take the study drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described in this appendix may be administered with the intent to treat the patient's malignancy.

Participants should be instructed to take the dose of abemaciclib every 12 hours. **Cycle length will be 28 days, even if treatment is held mid-cycle for toxicity.** The first cycle of abemaciclib will be dosed at 150 mg every 12 hours. If a patient has not required dose reduction(s) due to toxicity, then the dose of abemaciclib may be escalated at the start of Cycle 2 to 200 mg every 12 hours if the investigator determines that it is in the best interest of the patient.

Abemaciclib should be taken with a glass of water and consumed over as short a time as possible. Participants should swallow the tablets as a whole and not chew them. Participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A4 interaction. Additional drug administration instructions, including missed dose policy, are described in Section 6.2.8 of this appendix and are included in the abemaciclib participant pill diary (section 12 of this appendix).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires an abemaciclib dose delay of > 28 days from the previous dose, the participant must be discontinued from treatment completely. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen, MD at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Participants will keep a medication diary (see section 12 of this appendix). At the end of each

cycle, the diary will be returned and a new one will be given to the participant. Participants are to return all pill bottles and unused pills.

3.5 General Concomitant Medication and Supportive Care Guidelines

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

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

3.5.1 Strong CYP3A inhibitors and CYP3A inducers are **prohibited**. In vitro studies suggest that abemaciclib is a sensitive CYP3A4 substrate. Co-administration of abemaciclib with strong CYP3A4 inhibitors is predicted to increase the systemic exposure to abemaciclib; likewise CYP3A inducers can be expected to decrease systemic exposure to abemaciclib, possibly resulting in sub-therapeutic drug levels. Refer to Appendix C of master INSIGhT protocol for a list of prohibited drugs. Please note that this list may not be comprehensive.

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

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

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

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

3.5.6 Anti-seizure medications should be used as indicated. Only participants receiving non-EIAEDs are eligible (although protocol does allow for patients to register and initiate treatment with Temodar and radiation therapy while tapering off

EIAEDs). If for unavoidable clinical reasons (emergency department visit, severe allergies, toxicities, etc.) a participant's AED is switched to another AED, the following guidelines must be followed if applicable:

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

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

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

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

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

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

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

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

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

3.6 Guidelines for Diarrhea Management

At enrollment, participants 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 antidiarrhea therapy (eg loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (eg, 8-10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours
- If diarrhea does not resolve within antidiarrheal therapy within 24 hours to either baseline or Grade 1, then abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences the dose should be adjusted (see Table 4.2: Criteria for dose-modification and re-initiation of abemaciclib treatment).

3.7 Criteria for Taking a Participant Off Protocol Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported (3 months following last dose). If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

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

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Patrick Y. Wen, MD, at 617-632-2166 or pwen@partners.org.

3.8 Duration of Follow Up

Participants will be followed until death with monthly visits, telephone contact, or medical record review. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Refer to section 7 study calendar within this appendix for follow-up requirements and time points.

3.9 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

4. DOSING DELAYS/DOSE MODIFICATIONS

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

4.1 Anticipated Toxicities

In order for an event to be considered expected (known correlation to study drug/treatment) for the purposes of adverse event reporting, the event must be:

- Included in this section for Abemaciclib.
- Included in this section or included in the package insert or the informed consent document as a potential risk for Temozolomide and radiation therapy.

Note: For events that are secondary to an event deemed expected with a study agent/modality (e.g.

rectal pain or hypokalemia as a result of diarrhea or gait disturbance as a result of edema cerebral), please record as "possibly related to" and "expected with" the agent/modality.

4.1.1 Anticipated Toxicities for Radiation Therapy

A list of adverse events of all grades suspected to be radiation therapy treatment related, organized by CTCAE v4.03 category, includes:

- EAR AND LABYRINTH DISORDERS – external ear inflammation; other: dryness of ear canal; other: hardening of ear canal wax; external ear pain; other: hearing loss
- ENDOCRINE DISORDERS - other: hypophysitis, or hypopituitarism
- EYE DISORDERS – cataract; other: decreased vision
- GASTROINTESTINAL DISORDERS – nausea; vomiting
- GENERAL DISORDERS – fatigue
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – dermatitis radiation; injury other: optic nerve
- INVESTIGATIONS –lymphocyte count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED – treatment related secondary malignancy
- NERVOUS SYSTEM DISORDERS – headache; seizure; memory impairment; cognitive disturbance; somnolence; dysgeusia; central nervous system necrosis; edema cerebral; other: tumor inflammation**
- PSYCHIATRIC DISORDERS – personality change
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – scalp pain; other: scalp redness; alopecia

4.1.2 Anticipated Toxicities for Temozolomide

A list of adverse events of all grades suspected to be temozolomide treatment related, organized by CTCAE v4.03 category, includes:

- BLOOD AND LYMPHATIC SYSTEM DISORDERS – anemia; febrile neutropenia; bone marrow hypocellular
- GASTROINTESTINAL DISORDERS – constipation; nausea; vomiting; diarrhea
- GENERAL DISORDERS – gait disturbance; fatigue
- IMMUNE SYSTEM DISORDERS – allergic reaction
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – bruising; hemorrhage
- INVESTIGATIONS – neutrophil count decreased; lymphocyte count decreased; white blood cell decreased; platelet count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NERVOUS SYSTEM DISORDERS – dizziness; memory impairment; headache; seizure
- PSYCHIATRIC DISORDERS – insomnia
- REPRODUCTIVE SYSTEM AND BREAST DISORDERS – infertility
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – alopecia

4.1.3 Anticipated Toxicities for Abemaciclib

A list of adverse events of all grades suspected to be abemaciclib treatment related according to review of Investigator's Brochure, organized by CTCAE v4.03 category, includes:

- BLOOD & LYMPHATIC SYSTEM DISORDERS – white blood cell decreased; neutrophil count decreased; platelet count decreased; anemia
- GASTROINTESTINAL –diarrhea; dry mouth; nausea; vomiting; mucositis oral
- GENERAL DISORDERS- fatigue
- INFECTIONS & INFESTATIONS – conjunctivitis infective; pharyngitis; sinusitis; upper respiratory infection; urinary tract infection; vaginal infection
- INVESTIGATIONS – creatinine increased; weight loss; aspartate aminotransferase increased; alanine aminotransferase; GGT increased
- METABOLISM & NUTRITION DISORDERS – anorexia
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Muscle weakness (left-sided, lower limb, right-sided, trunk, & upper limb)
- NERVOUS SYSTEM DISORDERS – dizziness; dysgeusia
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – alopecia; pruritis
- VASCULAR DISORDERS – thromboembolic event

* "Generalized muscle weakness" to also include other CTCAE terms inclusive of a muscle weakness

** As CTCAE v. 4 recognizes 'Edema cerebral' only as a Gr4 event, please record events of 'Edema cerebral' deemed by Investigator to be Gr1-Gr3 or Gr5 as 'Nervous system disorders, Other: Tumor inflammation' (Gr1-Gr3 or Gr5, accordingly).

4.2 Dose Modifications/Delays for Temozolomide

4.2.1 No temozolomide dose reductions are allowed during the concomitant phase of treatment. If a participant experiences a toxicity related to temozolomide during the concomitant phase of treatment, then temozolomide dosing will be interrupted according the rules described in Table 4.2 of this appendix.

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

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

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

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

until resolution.

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

4.2.4.1 NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

4.2.5 Study teams are not required to hold for lymphopenia.

4.2.6 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 4.2 of this appendix, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of study treatment. All SAEs must be reported as detailed in Section 5.3 of this appendix.

Table 4.2: Criteria for dose-modification and re-initiation of temozolomide treatment

For toxicities attributable to temozolomide (considered at least possibly related), Table 4.2 should be adhered to as noted below. When the treating investigator feels that a hold of temozolomide is warranted for patient safety even though the toxicity is unlikely or unrelated to temozolomide, discussion with the Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Toxicity (organized per CTCAE v 4.03)		**Concomitant Temozolomide**
Neutropenia	**- Grade 2 (ANC 1.0 - 1.4 x 109/L)**	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level
	- Grade 3 (ANC 0.5 - 0.9 x 109/L)	
	- Grade 4 (ANC < 0.5 x 10^9/L)	Discontinue TEMOZOLOMIDE
Thrombocyto-penia	**- Platelet count: 50 - 99 x 10^9/L**	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, thenresume TEMOZOLOMIDE at the current dose level.
	- Platelet count: 10 - 49 x 10^9/L	
	- Platelet count: < 10 x 10^9/L	Discontinue TEMOZOLOMIDE
Non-hematologic toxicity	**- Grade 2 Except foralopecia, nausea, vomiting, constipation,weight loss, & anorexia)**	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.
	- Grade 3 Except foralopecia, nausea, vomiting, constipation)	Discontinue TEMOZOLOMIDE
	- Grade 4 Except foralopecia, nausea, vomiting, constipation)	Discontinue TEMOZOLOMIDE

4.3 Dose Modifications/Delays for Abemaciclib

All participants will be initially treated at Dose Level 0.

Abemaciclib Dose Levels

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

4.3.1 Table 4.3 should be adhered to for all toxicities considered at least possibly related to abemaciclib. If a participant experiences a toxicity unlikely or unrelated to treatment with abemaciclib, but may still warrant a hold or reduction of study drug for safety, discussion and approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

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

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

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

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

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

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

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

4.3.6.1 NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

4.3.7 Dose re-escalation (after dose reduction for toxicity) is never permitted in this study.

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

4.3.9 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in

Table 4.3, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of abemaciclib. All SAEs must be reported as detailed in section 5.3 of this appendix.

Table 4.3: Criteria for dose-modification and re-initiation of abemaciclib treatment

Table 4.3 should be adhered to for all toxicities attributable (considered at least possibly related) to abemaciclib as noted below. If a participant experiences a toxicity unlikely or unrelated to treatment with abemaciclib but may still warrant a hold or reduction of study drug for safety, discussion and written approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Toxicity (organized per CTCAE v4.03)	Actions
Investigations (for hyperglycemia, see *metabolism disorders*)	
ALT/SGPT or AST/SGOT - Grade 2 (>3.0- 5.0 x ULN)	First Occurrence: Interrupt until resolution to ≤ grade 1, then • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolution to ≤ grade 1 takes > 7 days, resume ABEMACICLIB at one lower dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
ALT/SGPT or AST/SGOT - Grade 3 (> 5.0 - 20.0 x ULN)	First Occurrence: Interrupt until resolution to ≤ grade 1, then • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolution to ≤ grade 1 takes > 7 days, resume ABEMACICLIB at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication. Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication.

ALT/SGPT or AST/SGOT **- Grade 4 (>20.0 x ULN)**	Interrupt ABEMACICLIB until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication.
Amylase, asymptomatic **- Grade 3 (> 2.0 - 5.0 x ULN)**	First Occurrence: Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1in ≤ 7 days, resume ABEMACICLIB at the current dose level; • If resolution to grade ≤1 in > 7 days, resume ABEMACICLIB at one lower dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Amylase **- Grade 4 (> 5.0 x ULN)**	Discontinue ABEMACICLIB
Bilirubin* **- Grade 2** **(>1.5 - 3 x ULN)**	First Occurrence: Interrupt ABEMACICLIB until resolution to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level; • If resolution to ≤ grade 1 takes > 7 days, resume ABEMACICLIB at one lower dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Bilirubin* **- Grade 3** **(> 3.0 – 10.0 x ULN)**	Interrupt ABEMACICLIB until resolution to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at one lower dose level; • If resolution to ≤ grade 1 takes > 7 days, discontinue ABEMACICLIB
Bilirubin **- Grade 4 (> 10.0 x ULN)**	Discontinue ABEMACICLIB
* For participants with a baseline hyperbilirubinemia of 1.0-1.5 x institution's ULN that is not felt to be clinically significant, the clinician may choose to continue ABEMACICLIB for elevations in total bilirubin that are two times the participant's baseline value (screening value). For total bilirubin that is greater than two times the baseline value, follow dose modification guidelines as outlined in the above table. However, in place of resolution to ≤ grade 1, ABEMACICLIB may resume once resolution to ≤ 2 x baseline value.	

Creatinine* **- Grade 2** **(>1.5 - 3 x ULN)**	First Occurrence: Interrupt treatment until resolution to ≤ grade 1, then • If resolved to ≤ grade 1 in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolution to ≤ grade 1 takes > 7 days, resume ABEMACICLIB decreased by one dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Creatinine * **- Grade 3** **(> 3.0 - 6.0 x ULN)** **- Grade 4 (> 6.0 x ULN)**	Discontinue ABEMACICLIB
* Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function.	
Lipase elevation, asymptomatic **- Grade 3 (> 2.0 - 5.0 x ULN)**	First Occurrence: Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level; • If resolution to grade ≤1 in > 7 days, resume ABEMACICLIB at one lower dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Lipase elevation, asymptomatic **- Grade 4 (> 5.0 x ULN)**	Discontinue ABEMACICLIB
Neutropenia **- Grade 3** **(ANC 0.5 - 0.9 x 109/L)** **- Grade 4** **(ANC < 0.5 x 10^9/L)** (see *Blood Disorders* for Febrile Neutropenia)	First Occurrence: Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 7 days, then resume ABEMACICLIB at the current dose level • If resolution to grade ≤1 in > 7 days, then resume ABEMACICLIB at one lower dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level

Thrombocytopenia **- Grade 3** **(PLT 25-49 x 10^9/L)**	First Occurrence: Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolution to grade ≤1 in > 7 days, then resume ABEMACICLIB at one lower dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Thrombocytopenia **- Grade 4** **(PLT < 25 x 10^9/L)**	Interrupt until resolved, then resume ABEMACICLIB at one lower dose level
Blood and lymphatic system disorders	
Febrile neutropenia **- ANC < 1.0 x 10^9/L with a single temperature of > 38.3 °C (101 F) or a sustained temperature of ≥ 38°C (100.4 F) for more than one hour**	Interrupt treatment until resolved, then resume ABEMACICLIB at one lower dose level. Febrile neutropenia should be managed promptly with broad-spectrum antibacterial therapy, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. Anemia and thrombocytoenpia should be treated supportively and if necessary, with red cell or platelet transfusions.
Gastrointestinal Disorders	
Diarrhea **- Grade 2** **(4-6 stools/day > pretx)**	Early treatment of diarrhea is recommended. Patients should be instructed to initiate anti-diarrheal therapy (such as loperamide) and notify the investigator at the first sign of loose stool. Investigators should assess the response of anti-diarrheal therapy within 24 hours of notification. If diarrhea can be controlled with optimal anti-diarrheal treatment within 24 hours to either baseline or grade 1, continue ABEMACICLIB. If not, interrupt treatment until resolved to ≤ grade 1, then resume ABEMACICLIB at the current dose (treating investigators may reduce by 1 dose level at their own discretion for first occurrence). If diarrhea returns as ≥ grade 2, then interrupt treatment until resolved to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Diarrhea **- Grade 3** **(≥7 stools/day > pretx)** **- Grade 4** **(urgent intervention indicated)** **(requires hospitalization)**	Early treatment of diarrhea is recommended. Patients should be instructed to initiate anti-diarrheal therapy (such as loperamide) and notify the investigator at the first sign of loose stool. Investigators should assess the response of anti-diarrheal therapy within 24 hours of notification. If diarrhea can be controlled with optimal anti-diarrheal treatment within 24 hours to either baseline or grade 1, continue ABEMACICLIB. If not, for diarrhea ≥ Grade 3, interrupt treatment until resolved to ≤ grade 1, then resume ABEMACICLIB at one lower dose level.

General Disorders	
Fatigue Grade 1 & 2	Maintain dose level. Initiating a stimulant agent is recommended.
Fatigue **- Grade 3**	First Occurrence: Interrupt ABEMACICLIB until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, resume ABEMACICLIB at the current dose level • If resolved in > 7 days, resume ABEMACICLIB at one lower dose level Second/Third Occurrence: • Interrupt until resolution to ≤ grade 1, then resume ABEMACICLIB at one lower dose level
Metabolism and Nutrition disorders	
Hypercalcemia **Grade 1-3**	Management of hypercalcemia per local institutional guidelines. ABEMACICLIB administration will continue daily. For patients requiring hospitalization for management of hypercalcemia, ABEMACICLIB administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Hypercalcemia **Grade 4**	Management of hypercalcemia per local institutional guidelines. ABEMACICLIB administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Hyperuricemia **Grade 1-4**	Management of hyperuricemia per local institutional guidelines. ABEMACICLIB administration will continue daily. If grade 4 persists > 14 days despite medical management, ABEMACICLIB administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Hypophosphatemia **Grade 1-4**	Initiate phosphorous supplementation daily. ABEMACICLIB administration will continue daily. If grade 4 persists > 14 days despite medical management, ABEMACICLIB administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Nervous system disorders	
Neurotoxicity ≥ 1 CTCAE grade level increase, attributable to drug	Maintain dose level
Neurotoxicity ≥ Grade 3, attributable to drug	Interrupt ABEMACICLIB until resolved to ≤ grade 1 or baseline, then resume ABEMACICLIB at one lower dose level

Skin and subcutaneous tissue disorders	
Any Rash Grade 1	Maintain dose level. Consider initiating appropriate skin toxicity therapy such as antihistamines.
Any Rash Grade 2	Maintain dose level. Initiate/intensify appropriate skin toxicity therapy such as antihistamines.
Any Rash Grade 3	Interrupt ABEMACICLIB until resolution to CTCAE Grade ≤ 1, then: • If resolved in ≤ 7 days, resume ABEMACICLIB at one lower dose level • If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue participant from study drug treatment.
Any Rash Grade 4	Discontinue ABEMACICLIB
Other unspecified RELATED adverse events	
Other unspecified Grade 1 and 2 events considered at least possibly related to ABEMACICLIB	Maintain treatment with ABEMACICLIB
Other unspecified clinically significant Grade 3 clinically significant events considered at least possibly related to ABEMACICLIB	Interrupt treatment until resolution to ≤ grade 1 or returned to baseline, treatment may resume at the same dose level or a 1 dose level decrease, at the investigator's discretion. Continuation of ABEMACICLIB is permitted upon recovery to stable Grade 2 if the investigator and overall principal investigator (Dr. Patrick Y. Wen) agree that the event is not considered clinically significant.
Other unspecified Grade 4 events considered at least possibly related to ABEMACICLIB	Discontinue ABEMACICLIB

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (section 4.1 of this appendix) and the characteristics of an observed AE (Section 5.2 of this appendix) will determine whether the event requires expedited reporting **in addition** to routine reporting.

This section specifies reporting requirements to the FDA, Overall PI/Coordinating Center, DF/HCC IRB, and manufacturer as applicable.

5.1 Expected Toxicities

Refer to section 4.1 of this appendix for expected toxicities for assigned study treatment arm.

5.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in section 4.1 of this appendix should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

- **Serious Adverse Event (SAE) Definition**:
  A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:
    - Results in death
    - Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
    - Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
    - Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
    - Is a congenital anomaly/birth defect;
    - Constitutes an important medical event. Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

5.3 Expedited Adverse Event Reporting

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

5.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical that is *Serious, Unexpected,* and there is a *Reasonable Possibility* (i.e., possible, probable, or definitive attribution) the Adverse Event is related to the study intervention.

5.3.3 **Expedited Reporting Guidelines to Overall PI/Coordinating Center**

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

External investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the AE form should be forwarded to the Overall PI within the timeframes detailed in the table below. The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

In addition to local IRB reporting policies, all sites are required to following the Table 5.3.3 expedited reportable AE requirements:

NOTE: Until patients initiate treatment with Abemaciclib on study, please report per Table 5.3.3 'Expedited AE Reporting by external sites to Coordinating Center/Overall PI' of Appendix E (Control Arm).

Table 5.3.3 Expedited AE Reporting Requirements

Adverse Event Characteristics				Reporting Requirement	
Serious-ness	**Toxicity**	**Known Correlation[f]**	**Attribution to Abemaciclib**	**Eli Lilly and Company - Via Fax or Email[c] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**	**Overall PI (Patrick Y. Wen, MD) at the DFCI Coordinating Center Via Email [b] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**
Serious[e]	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [a]	Within 24 hours from notification [a]
Non-Serious	Grade 4	Any (Expected or Unexpected)	Any	Not Required	Within 5 working days from notification [a]
Non-Serious	Grade 2 or 3	Unexpected	Possible, probable, definite	Not Required	Within 7 working days from notification [a]

a. In the event that the participating investigator/site team does not become aware of an adverse event requiring expedited reporting immediately (e.g., participant sought treatment elsewhere), the participating investigator/site team is to report the event within the required hours/days noted above after learning of it and document the time of his or her first awareness of the adverse event. The initial report must be as complete as possible, including assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE or reportable AE is required.
b. Email the Medwatch 3500A form, reportable AE coversheet (section 10 of this appendix), and the local IRB SAE report (if applicable) to the DFCI Coordinating Center with the subject title as "INSIGHT SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Patrick Y. Wen, and to the DFCI Coordinating Center personnel.
c. Reportable AE Coversheet is found in section 10 of this appendix. The coversheet contains all FAX numbers/e-mails and needed for reporting purposes.
d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm
e. Seriousness is defined in section 5.2 of this appendix.
f. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Anticipated Toxicities list (protocol section 4.1 of this appendix) which is derived from the Investigator's Brochure and/or package insert (if applicable).

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

1. Document/describe reportable AE(s) on the following:
    a. MedWatch 3500A
        i. downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. DFCI Reportable AE Coversheet – INSIGhT Abemaciclib Arm
        i. Coversheet can be found in section 10 of this appendix. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.
2. Scan and email above documents to NeuroOnc_SAE@dfci.harvard.edu with the subject title "INSIGHT SAE"
    a. All AE reports received at this account are forwarded immediately to Overall Principal Investigator (Dr. Patrick Y. Wen), and to Coordinating Center personnel.
    b. If available and applicable, also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.

5.3.5 Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

- Lymphopenia (grades 2-4)
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for treatment of patient's underlying disease after coming off study treatment (e.g. admission after patient is removed from active study treatment for craniotomy)

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

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

5.5 Expedited Reporting to Hospital Risk Management

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

5.6 Routine Adverse Event Reporting

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

PHARMACEUTICAL INFORMATION

Temozolomide

6.1.1 Description

The chemical name of Temozolomide is 3,4-dihydro-3methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide and the molecular weight is 194.15, which acts as an alkylating agent.

In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 1.6 to 1.88 hours. Following oral administration, the drug, Temozolomide, is rapidly absorbed and then hydrolyzed to the active metabolite 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC spontaneously degrades to CO_2 and 5-aminoimidazole-4-carboxamide (AIC) and excreted via the urine. CYP isoenzymes play an only minor role in Temozolomide metabolism.

6.1.2 Form

Temozolomide drug will be supplied commercially and should be ordered per local policy. The drug products are stable when stored according to instructions on the label.

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of Temozolomide and the inactive ingredients sodium starch glycolate, tartaric acid, stearic acid, and colloidal silicon dioxide.

The body of the capsules is made of gelatin, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength.

6.1.3 Storage and Stability

Temozolomide is stable at room temperature.

6.1.4 Compatibility

There are no known compatibility issues.

6.1.5 Handling

Routine chemotherapy handling is recommended.

6.1.6 Availability

Temozolomide is available through special pharmacy and can be prescribed by the treating physician.

6.1.7 Preparation

None

6.1.8 Administration

- Temozolomide capsules should not be opened or chewed; they must be swallowed whole with a glass of water one hour before or after food and other medications.
- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.
- If the participant forgets to take his/her temozolomide dose more than 10 hours from the last dose, then that dose should be withheld and temozolomide should be restarted at the time of the next planned dose.

6.1.9 Ordering

Temozolomide drug will be supplied commercially and should be ordered per local policy.

6.2 Abemaciclib

6.2.1 Description

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

In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 17 to 38 hours. Following oral administration, abemaciclib was extensively metabolized

followed by biliary excretion of metabolites. Strong CYP3A inhibitors may increase abemaciclib exposures, and strong inducers may decrease abemaciclib exposures. Caution should be exercised when coadministering abemaciclib with narrow therapeutic drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A.

6.2.2 Form

Abemaciclib drug product will be supplied for clinical trial use as abemaciclib with excipients in hypromellose tablets. The drug products are stable when stored accordingto instructions on the label.

Abemaciclib will be supplied as 50 mg hypromellose tablets as follows:

- a white hypromellose capsule containing 50 mg of abemaciclib and the inactive ingredients pregelatinized starch, dimethicone, and colloidal silicon dioxide.

6.2.3 Storage and Stability

Abemaciclib is stable at room temperature.

6.2.4 Compatibility

There are no known compatibility issues.

6.2.5 Handling

Routine chemotherapy handling is recommended.

6.2.6 Availability

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

6.2.7 Preparation

None.

6.2.8 Administration

- Abemaciclib will be administered at a starting dose of 150 mg every 12 hours. If a patient has not required dose reduction(s) due to toxicity, then the dose of Abemaciclib may be escalated at the start of Cycle 2 to 200 mg every 12 hours if the investigator determines that it is in the best interest of the patient. Participants should fast one hour before and one hour after each dose. Participants should be instructed to take their doses, twice a day, at approximately the same times each day and approximately 12 ± 3 hours apart.

- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.
- If the participant forgets to take his/her abemaciclib dose more than 3 hours from the last dose, then that dose should be withheld and abemaciclib should be restarted at the time of the next planned dose.

6.2.9 **Ordering**

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

6.2.10 **Accountability**

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

6.2.11 **Destruction and Return**

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

7. STUDY CALENDAR

Assessment	Screen-ing[a]	Concomitant							Rest[e]	Adjuvant Cycles		End of Tx[h]	30-Day Post Drug[i]	Active Follow-Up[j]	Long Term Follow-Up[k]
		D1[b]	D8[c]	D15[c]	D22[c]	D29[c]	D36[c]	D43-49[d]		D1[f]	D15[g]				
Informed Consent[l]	X														
Medical History[m]	X														
Inclusion/Exclusion Criteria[n]	X														
Vital signs[o]	X	X			X			X		X		X			
Physical Exam	X	X			X			X		X		X			
Neurologic Exam	X	X			X			X		X		X			
Karnofsky Performance Status[p]	X	X			X			X		X		X			
Concomitant Medications[q]	----------X----------														
Adverse Events[r]		----------X----------													
Pregnancy Test (β-HCG)[s]	X	X			X					X		X			
Coagulation[t]	X														
Hematology[u]	X	X	X	X	X	X	X	X	X[cc]	X		X			
Serum Chemistry[v]	X	X			X			X	X[cc]	X[v]	X[v]	X[v]			
EKG[w]	X									X		X			
Radiation[x]		----------X----------													
Temozolomide		----------X----------													
Abemaciclib										----------X----------					
Imaging – MRI[y]	X	X								X		X		X	
Response Assessment[z]										X		X		X	
Post-treatment therapies[aa]														X	X
Survival[bb]														X	X

a. All screening procedures to be performed within 28 days of initial registration. **NOTE: refer to section 10 of master protocol for comprehensive details on screening assessments, initial registration, randomization assignment and second registration timing.**

b. Concomitant radiation and temozolomide must begin no later than 42 days following initial surgery. Day 1 assessments must be performed within 3 days of starting study treatment. Screening assessments may be utilized as baseline/Day 1 assessments if they fall within window.

c. +/- 2 day window for weekly assessments during concomitant phase.

d. Day 43-49 visit to occur within +/- 7 days of completing radiation.

e. Rest period is 28-42 days.

f. Adjuvant C1D1 to begin >28 (+14) days following end of radiation. Cycle 1, Day 1 adjuvant assessments to be performed within 4 days of Day 1 abemaciclib. All adjuvant cycle 1, day 1 assessments must be resulted and reviewed prior to initiating treatment with abemaciclib; participants cannot begin adjuvant abemaciclib if they meet any criteria requiring a dose modification as outlined in section 4.3 of this appendix. **Adjuvant cycles will be 28 days even if treatment is held.** Day 1 assessments for subsequent adjuvant cycles to be performed within 4 days prior to Day 1 abemaciclib. (If utilizing the assessment window, that does *not* shorten the previous cycle or extend the upcoming cycle; each = 28 days.)

g. Day 15 assessments required for adjuvant Cycle 1 visit only.
h. End of Treatment: assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment.
i. 30-Day Post Drug: a contact/visit is to be performed 30 days (+7 days) after date of last drug taken on study. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last drug.
j. Active Follow-Up: participants who discontinue study treatment for reasons other than disease progression will be followed every 4 weeks (+/-1 week) via contact or medical record review andstudy team must continue monitoring participant's disease status by radiologic imaging at 8 week intervals (+/- 1 week) until (1) documented disease progression, (2), death, (3) participant withdraws from follow-up, or (4) end of study, whichever occurs first.
k. Long Term Follow-Up: participants will be followed every 4 weeks (+/-1 week) via contact or medical record review until death. Participants must be followed for survival data at every long-term follow-up time point and for post-treatment therapies and reason for stopping those therapies when available.
l. Informed Consent: must be obtained by MD attending. No study specific screening procedures may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration. Following initial registration and receipt of INSIGhT randomization assignment, participants must be sign the consent form specific to the assigned treatment arm prior to initiating treatment for that study arm.
m. Medical History: to include review of treatment history for GBM, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
n. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements for initial registration. See section 2 of this appendix for arm specific eligibility criteria.
o. Vital Signs: weight, heart rate, blood pressure, respiration rate, temperature. Vital signs must be performed prior to administration of treatment on treatment days. Height required only at screening.
p. Karnofsky Performance Status (KPS): see appendix A of master protocol.
q. Concomitant Medications: concomitant medications and reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.
r. Adverse Events: adverse events experienced by participants will be collected and recorded from the first dose of treatment on-study up to the 30-Day Post Drug Visit of the last dose of study medication (+ 7 days depending on when 30-Day Post Drug visit/contact occurs).
s. Pregnancy Test: required for women of child bearing potential (see section 3 of master protocol for definition of women of child bearing potential).).
t. Coagulation: PT/INR, PT, PTT required at screening only.
u. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
v. Serum Chemistry: albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed). **In addition, LDH, uric acid, amylase, lipase and phosphorus are required during adjuvant cycles and End of Treatment chemistry time points.**
w. EKG: required at screening, adjuvant C2D1 and End of Treatment visit.
x. Radiation: see section 3.1 of this sub-study appendix for definition of standard radiation therapy per protocol.
y. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site, Appendix D Recommended MRI Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial. Local reading (investigator assessment) will be used to determine eligibility and for participant management. Adjuvant C1D1 imaging should be performed within 7 days prior to starting adjuvant treatment; subsequent imaging should be performed within 7 days prior to Day 1 of odd cycles.
z. Response Assessment: Per RANO criteria (see section 11 of master protocol).
aa. Post-treatment Therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected when available.
bb. Survival: date of death and reason must be collected for overall survival purposes.
cc. Hemes & Serum Chemistries will be done as per SOC during patient's post-RT rest phase: hemes = weekly; chemistries need only be performed @ the end of RT visit and prior to adjuvant C1D1 (unless clinically indicated otherwise)

8. MEASUREMENT OF EFFECT

Refer to section 11 of master INSIGhT protocol for details on measurement of effect.

9. REFERENCES

Ortega, S., et al. (2002). "Cyclin D-dependent kinases, INK4 inhibitors and cancer." Biochimica et biophysica acta **1602**(1): 73-87.

Sherr, C. J. (1996). "Cancer Cell Cycles." Science (New York, NY) **274**(5293): 1672-1677.

Stupp, R., et al. (2005). "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma." N Engl J Med **352**(10): 987-996.

10. DFCI REPORTABLE AE COVERSHEET – INSIGHT ABEMACICLIB ARM

DF/HCC Protocol No. 16-443

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this AE):

☐ Dr. Patrick Y. Wen and Dana-Farber Coordinating Center
Email: NeuroOnc_SAE@dfci.harvard.edu

☐ Eli Lilly and Company Fax: 866-644-1697; Email: MAILINDATA_GSMTINDY@LILLY.COM

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

Participant # and Initials:	
Date Event Met Reporting Criteria (as defined in protocol):	
Type of Report: ☐Initial ☐Follow-up	Hospitalization: ☐ YES ☐ NO

CTCAE Event #1 Description:	CTCAE Event #2 Description (if applicable): *NOTE: use another coversheet if more than 2 events are being reported at this time*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death
Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness to **Temozolomide**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Temozolomide**: ☐Expected ☐Unexpected
Attribution to **Temozolomide**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Temozolomide**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness to **Abemaciclib**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Abemaciclib**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Abemaciclib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Abemaciclib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Reporting Investigator (print):	

Signature of Reporting Investigator:_____ Date:_____

11. TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Take_____capsule(s) at_____mg strength +_____capsule(s) at_____mg strength

+_____capsule(s) at_____mg strength

This treatment diary is for you to indicate that you took the study drug as prescribed. **Please bring this treatment diary and your pill bottle(s) with you to each clinic visit. At the end of the cycle, please sign and date the bottom of the treatment diary.**

Temodar Instructions

During radiation therapy, **Temodar** should be taken daily (including weekends and holidays) – your Clinical Team will confirm the total # of days you will take Temodar**.**

- Temodar capsules should be taken whole (do not chew or open capsules), two to three hours prior to radiation with a full glass of water on an empty stomach (one hour before or after food and other medications).
- If you realize you have missed a dose by more than 10 hours, the dose should not be retaken and the next dose should not be increased to make up for the missed dose. Please indicate missed doses on this diary.
- If a dose is vomited, the capsules are not to be replaced and you can indicate this vomited dose on the diary.
- On days when you do not have radiation, Temodar should be taken in the morning on an empty stomach (one hour before or after food and other medications) with a full glass of water.
- If your course of radiation extends beyond 42 days because of delays, the course of Temodar may be extended to a maximum of 49 days.

Please check with your study treatment team if you have any questions regarding how or when you should take your Temodar doses.

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials
DAY 8	**DAY 9**	**DAY 10**	**DAY 11**	**DAY 12**	**DAY 13**	**DAY 14**
Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials
DAY 15	**DAY 16**	**DAY 17**	**DAY 18**	**DAY 19**	**DAY 20**	**DAY 21**
Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Participant/Guardian Signature: _____ Date: _____

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 22	DAY 23	DAY 24	DAY 25	DAY 26	DAY 27	DAY 28
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 29	**DAY 30**	**DAY 31**	**DAY 32**	**DAY 33**	**DAY 34**	**DAY 35**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 36	**DAY 37**	**DAY 38**	**DAY 39**	**DAY 40**	**DAY 41**	**DAY 42**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Participant/Guardian Signature:_____ Date: _____

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 43	DAY 44	DAY 45	DAY 46	DAY 47	DAY 48	DAY 49
Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials

Participant/Guardian Signature:_____ Date: _____

12. ABEMACICLIB DOSING INSTRUCTIONS & DRUG DIARY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Cycle #:_____Month & Year:_____Abemaciclib Dose:_____mg, two times a day.

TAKE_____pill(s) in the morning and_____pill(s) in the evening.

Abemaciclib Description:

- Your study drug (Abemaciclib) is supplied as 50 mg white, capsule

Abemaciclib Instructions – When and How:

- Take study drug (Abemaciclib) twice a day, once in the morning and once in the evening.
- Take the drugs at approximately the same time each morning and evening, so that you are taking the drugs 12 hours apart.
- Fast one hour before and one hour after each dose. Take the pill(s) with a glass of water and swallow them whole; do not chew them or crush them.
- Do not skip any doses.
- If you forget to take your pills in the morning you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time in the evening (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you forget to take your pills in the evening, you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time the next morning (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you vomit your pills, write this down in your pill diary. Do not take a replacement dose. Take the next scheduled dose as usual (one dose only). Please call your study nurse or doctor to discuss vomited doses.

Additional Instructions:

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

To be completed by study personnel: Patient ID #________Patient Initials:________Month & Year:___________Temodar Dose:____________mg

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

Participant/Guardian Signature: ____________________________________ Date: __________________

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

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

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

Participant/Guardian Signature:_____ Date: _____

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

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

APPENDIX G CC-115 ARM OF INSIGHT

TABLE OF CONTENTS

1. BACKGROUND

1.1 CC-115 (CC0483115)

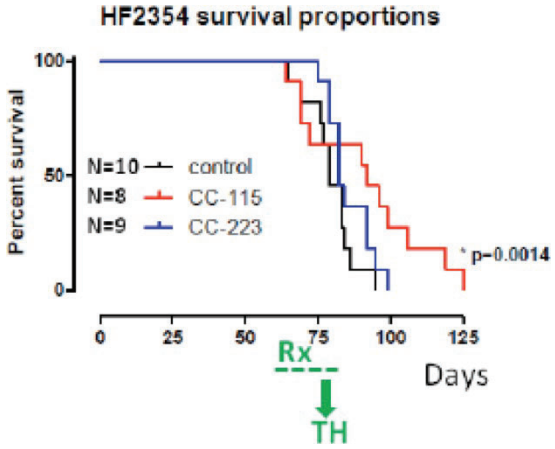
Rationale & Proposed Biomarker Association

CC-115 (CC0483115) is a potent and selective oral dual inhibitor of mammalian target of rapamycin (mTOR) kinase (both mTORC1 and mTORC2) and deoxyribonucleic acid-dependent protein (DNA PK) kinase (dual DNA-PKi/TORKi) that is in development for the treatment of solid and hematologic malignancies [Mortensen 2015]. The PI3K/Akt/mTOR signaling axis plays a central role in cell growth, survival, motility, and metabolism in a variety of cancers [Fruman 2014, Engelman 2009], including GBM [Brennan 2013]. DNA-dependent protein kinase is a serine/threonine kinase involved in the repair of DNA double strand breaks [Collis 2005, Bozulic 2008, Surucu 2008], which are considered to be the most lethal DNA lesion and the main driver of cellular death following treatment with ionizing radiation. Therefore, beyond its hypothesized growth-inhibitory effect as monotherapy, CC-115 has the potential to be a radiation sensitizing agent in the treatment of GBM [Zhao 2006]. There is no preclinical or clinical data to suggest a genomic subgroup which will be more likely to respond to treatment, but given the *a priori* hypothesis based on mechanism of action, we will consider aberrations to the PI3K pathway while evaluating treatment efficacy.

Preclinical data

The distribution of CC-115 into brain was investigated in male WT FVB mice and male MDR 1 a/b KO mice (Report CC-115-DMPK-009). Following a single oral gavage dose of 5.0 mg/kg of CC-115, plasma exposure of CC-115 was similar in WT and KO mice. Brain exposure of CC-115 was 11% and 21% of plasma exposure in WT and KO mice, respectively. The brain to plasma ratio of exposure to CC-115 in KO mice was 1.9-fold higher than that in WT mice. These results suggest that P-gp contributed to some extent to the limited brain exposure of CC-115.

CC-115 inhibited U87MG xenograft tumor growth in a dose-dependent manner. The minimum dose required to obtain approximately 65% tumor volume reduction compared with vehicle control was 0.5 mg/kg QD. Significant inhibition of mTOR pathway markers S6RP and AKT (S473) was observed in tumor samples following a single oral dose of CC-115, indicating that the antitumor activity was mediated through the inhibition of both mTORC1 (S6RP) and mTORC2 (AKT [S473]).



Using a GBM orthotopic PDX model with unmethylated MGMT promoter, single agent CC-115 extended the survival of mice and was beyond that seen with mTORC1/2 inhibition alone (CC-223) (Figure 1). No effects were seen in another model where MGMT was methylated (data not shown). CC-115 showed synergy in combination with ionizing radiation in several GBM neurosphere models *in vitro* (Figure 2) and enhanced the ability of radiation to limit tumor growth *in vivo* (Figure 3). Additional in vivo data has shown that radiation induces DNA-PK expression in GBM xenografts as part of the DNA damage response and that this response is attenuated with CC-115.

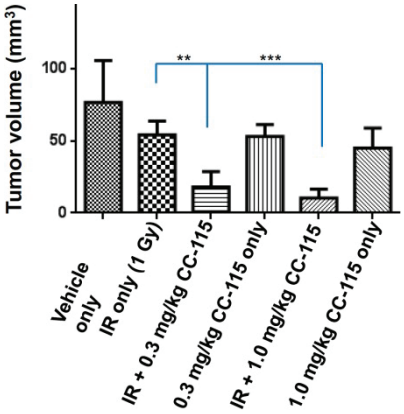


Figure 1: Improved survival in MGMT-unmethylated GBM Patient Derived Xenograft (PDX) orthotopic model. CC-115 Dual PNA-PK/mTORC1/2i; CC-223 mTORC1/2i (Bergman et al. AACR 2015).

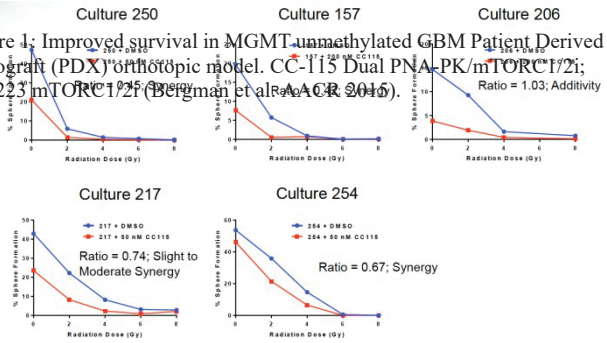


Figure 2: *In vitro* neurosphere formation assay demonstrating additivite or synergistic effect of CC-115 in combination with RT

Figure 3: CC-115 in combination with RT is more effective than either RT or CC-115 alone in limiting tumor growth in an *in vivo* GBM model.

Clinical data

One Phase 1a/1b multicenter open-label clinical study (CC-115-ST-001) demonstrated the maximum tolerated dose of CC-115 to be 40 mg QD and 15 mg BID, with near maximal inhibition of pAKT and partial inhibition of p4EBP1 at 10 mg BID. Durable mTOR inhibition throughout the dosing period was observed with the BID dosing schedules and was more pronounced at the maximum tolerated dosing schedule of 10 mg BID when compared with 25 mg QD. DLTs in the BID cohorts were transaminase increase and stomatitis (15 mg BID). While preclinical studies suggested limited blood-brain penetration, CC-115 showed reasonable penetration into GBM tissue in a surgical expansion cohort at 10 mg bid with a median GBM/plasma ratio of ~0.35 (0.04-1.71) (Table 1).

Table 1: Surgical expansion cohort demonstrating reasonable penetration of CC-115 into GBM at 10mg bid.

Tissue Type	Time (h)	Subject 003-1017	Subject 012-1001	Subject 012-1002	Subject 012-1003	Subject 012-1004	Subject 202-1004	Subject 203-1006	Subject 203-1011
GBM (ng/g)	1.5	96.5	26.0	30.6	11.8	57.6	17.8	74.6	4.01
Plasma (ng/mL)	1.5	101	86.6	91.6	32.5	44.4	NS	43.8	109
GBM/ Plasma	NA	0.95	0.30	0.33	0.36	1.30	NA	1.71	0.04

Given the therapeutic hypothesis of radiosensitivity supported by preclinical data, CC-115 (10 mg bid) will replace TMZ in both the concurrent and adjuvant phase of treatment. As this dose has never been combined with radiation therapy, we will conduct a safety lead in with the combination prior to expansion to the full phase II. Should this dose be found to be too toxic in combination with radiation, we will enroll one dose level lower. Should that combination be found too toxic, the combination will no longer be considered for further testing in combination with radiation therapy. In this case, the protocol will be amended to allow patients to receive radiation therapy with concomitant temozolomide followed by adjuvant single agent CC-115.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria Specific to the CC-115 Arm

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration (section 4 of master protocol). Once the randomization assignment has been received following initial registration, all participants randomized to the CC-115 arm must meet the following criteria prior to participating in the CC-115 arm of the study.

2.1.1 Participants must be willing and able to provide written informed consent for the CC-115 arm of the INSIGhT trial.

2.1.2 Women of child bearing potential (women who are not free from menses for > 2 years, post hysterectomy/oopherectomy, or surgically sterile) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from date of intial dose and for 28 days following the last dose of CC-115. Men (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in sexual activity with a woman of child bearing potential from date of initial dose and for 28 days following the last dose of CC-115.

2.2 Second INSIGhT Registration: Registration to CC-115 Arm

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. Registration to the CC-115 arm must occur following initial registration to master INSIGhT protocol and receipt of randomization assignment, and prior to the initiation of protocol therapy. Any participant not registered to their protocol specific assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria in section 2.1 of this sub-study appendix and a member of the study team will complete the protocol-specific eligibility checklist.

Following initial registration, any additional laboratory assessments prior to start of treatment will not be used to re-confirm eligibility. Refer to section 4 of this appendix for toxicity management between registration and start of study treatment.

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

2.2.1 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

2.2.2 Registration Process for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. The required forms for registration can be found in Appendix B.

Following registration, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Refer to Appendix B, Section 3.7 for registration details.

3. TREATMENT PLAN

Participants treated on the CC-115 arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix with concomitant twice daily oral dosing of CC-115, subsequently followed by continuous twice daily oral dosing of CC-115. Patients will not receive either concurrent or adjuvant temozolomide. Given the therapeutic hypothesis of radiosensitivity supported by preclinical data, an initial safety lead-in will be conducted as described in section 3.3 below.

3.1 Definition of Standard Radiation Therapy

The patient must undergo MRI based treatment planning (CT with contrast-based planning only if patient unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). The margin may be reduced around natural barriers to tumor growth, and also to allow sparing of organs at risk, if necessary. The volume must be treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast-enhancing region is acceptable. Treatment or no treatment of the T2/FLAIR abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 52 calendar days. Maximum dose (defined as a volume greater than 0.03 cc) to critical structures include: 60 Gy to the brainstem, 56 Gy to the optic chiasm, 55 Gy to the optic nerves, and 50 Gy to the retinae.

Participants are permitted to have radiotherapy as described in this section performed at any NCI funded cooperative group site. Prospective Overall PI approval, or approval by his designee (other Coordinating Center radiation oncologists), is required for any radiotherapy site that is not an NCI funded cooperative group site. At the discretion of the DFCI Coordinating Center, a radiation plan may be requested to be prospectively approved for a non-NCI site prior to initiating radiotherapy at the site. Any questions regarding permitted radiotherapy sites should be directed to the DFCI Coordinating Center or Overall PI Patrick Y. Wen, MD.

3.2 Treatment Regimen – CC-115 Administration

The study drug, CC-115, will be administered on an outpatient basis. The investigator will instruct the participant to take the study drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Participants should be instructed to take the oral dose of 10 mg CC-115 every 12 hours. CC-115 should begin the same day as the participant's radiation therapy and continue through radiation until beginning of adjuvant CC-115 cycles. The initial 10 weeks on-study will be referred to as the initiation cycle (approximately 6 weeks of RT + CC-115, followed by 4 weeks of CC-115) and after the initial 10-weeks cycles will be referred to as adjuvant cycles. **Adjuvant cycle**

length will be 28 days, even if treatment is held mid-cycle for toxicity, and there will be no rest period between cycles. If a participant, including safety lead-in participants, is dose reduced during the initial 10 weeks of treatment, then the dose of CC-115 may be escalated one dose level at the start of adjuvant Cycle 2if the investigator determines that it is in the best interest of the participant.

CC-115 should be taken orally with water and consumed over as short a time as possible. Each morning dose will be taken with water and each evening dose (taken approximately 12 hours after the morning dose) should be taken with water. CC-115 may be taken up to 3 hours late if dosing has been delayed on a single day; otherwise that dose should be omitted.

Participants should swallow the capsules as a whole and not chew them. Participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A4 interaction. Additional drug administration instructions, including missed dose policy, are described in section 6.1.8 of this appendix and are included in the participant pill diary (section 11 & section 12 of this appendix).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires a CC-115 dose delay of > 28 days from the previous dose, the participant must be discontinued from treatment completely. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Participants will keep a medication diary (see sections 11 & section 12 of this appendix). At the end of each cycle, the diary will be returned and a new one will be given to the participant. Participants are to return all pill bottles and unused pills.

3.3 Safety Lead-In

Because there is no safety data available for CC-115 in combination with radiotherapy, a safety lead-in will be conducted utilizing a 3+3 design, including 3-6 patients in each cohort, to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of CC-115 when administered with radiation therapy. The MTD will be defined as the dose at which ≤ 33% of patients experience a DLT and the MTD/RP2D CC-115 dose will then be incorporated into the phase II portion of the arm. The first 12 participants enrolled to this arm will be considered as safety lead-in and observed for DLTs for 10 weeks (see section 3.4 below for DLT definitions) as follows:

- If at Dose Level 0, ≤ 1 of the first 3 participants develop a DLT, 3 more participants will be enrolled at Dose Level 0. Then, if ≤ 2 of the 6 participants treated at Dose Level 0 experience a DLT, an additional 6 participants will be enrolled at Dose Level 0. Then, if ≤ 3 of the 12 participants treated experience a DLT, Dose Level 0 will be considered the MTD.

- If at Dose Level 0, > 1 of the first 3 participants , > 2 of the first 6 participants or > 3 of the first 12 participants develop a DLT, enrollment to Dose Level 0 will stop and subsequent enrollment will begin at Dose Level -1.
- If at Dose Level -1, ≤ 1 of the first 3 participants develop a DLT, 3 more participants will be enrolled at Dose Level -1. Then, if ≤ 2 of the 6 participants treated at Dose Level -1 experience a DLT, an additional 6 participants will be enrolled at Dose Level -1. Then, if ≤ 3 of the 12 participants treated experience a DLT, Dose Level -1 will be considered the MTD.
- If at Dose Level -1, > 1 of the first 3 participants, > 2 of the first 6 participants, or > 3 of the first 12 participants develop a DLT, enrollment to Dose Level -1 will stop and subsequent enrollment will begin at Dose Level -2.
- If at Dose Level -2, ≤ 1 of the first 3 participants develop a DLT, 3 more participants will be enrolled at Dose Level -2. Then if ≤ 2 of the 6 participants treated at Dose Level -2 experience a DLT, an additional 6 participants will be enrolled at Dose Level -2. Then if ≤ 3 of the 12 participants treated experience a DLT, Dose Level -2 will be considered the MTD.
- If at Dose Level -2, > 1 of the first 3 participants, > 2 of the first 6 participants, or > 3 of the first 12 participants treated at Dose Level -2 experience a DLT, administration of CC-115 in combination with radiation therapy and the appendix will be amended to allow patients to receive therapy with concomitant temozolomide followed by adjuvant single agent CC-115.

Table: Safety Lead-In CC-115 Dose Levels

Dose Level	Dose of CC-115
0 (starting dose)	10 mg every 12 hours
-1	7.5 mg every 12 hours
-2	5 mg every 12 hours

3.4 Definition of Dose-Limiting Toxicity (DLT)

A DLT is defined as a clinically significant adverse event considered at least possibly related to CC-115 and meets any of the criteria below during the first 10 weeks of study treatment (referred to as the initiation cycle). If a participant comes off for reasons other than a dose-limiting toxicity during the DLT period, he/she will be replaced.

Dose limiting toxicities are defined below. A DLT must have an attribution of possible, probable, or definite to CC-115 and meets the below criteria. For patients experiencing a DLT during the safety lead-in portion of the study, CC-115 must be discontinued. If there is any question concerning a DLT, sites should contact the DFCI Coordinating Center to determine patient's DLT status. The Coordinating Center with the Overall PI will make the final decision.

- Hematological toxicities will be considered dose limiting if any of the following occur (grade 3 or 4 lymphopenia will not be considered a DLT):
    - ANC of < 500/mm^3 for > 7 days
    - Platelets < 25,000/mm^3 for > 48 hours or platelets < 50,000/mm^3 with clinically significant bleeding
    - ≥ Grade 3 febrile neutropenia (ANC < 1.0 × 10^9/L and fever > 101°F/38.3°C)
    - Any hematologic toxicity that prevents administration of CC-115 for > 28 days
- Non-hematological toxicities will be considered dose limiting if any of the following occur:
    - Inability to complete ≥ 75% of RT due to toxicity related to or exacerbated by CC-115 added to Radiation Therapy.
    - Grades 3-4 severity, with the following exceptions:
        - Nausea, vomiting, and diarrhea without sufficient prophylaxis
        - Grade 3 hyperglycemia lasting ≤ 4 days (with optimal medical management) and grade 4 hyperglycemia lasting < 12 hours (with optimal medical management)
        - ≥ grade 3 rash of the acneiform or maculopapular type for no more than a 4 day duration (with optimal medical management)
        - Grade 3 electrolyte disturbances that are asymptomatic and that respond to replacement or intervention (e.g. IV fluids) within 48 hours
        - Grade 3 neurologic toxicity responding within two weeks to steroids, anticonvulsants, or electrolyte correction
        - A subject's first episode of deep venous thrombosis (DVT) or pulmonary embolism will not require dose modification or be considered a DLT since this is very common in glioblastoma patients

3.5 General Concomitant Medication and Supportive Care Guidelines

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

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

3.5.1 Strong CYP3A inhibitors and CYP3A inducers are **prohibited**. In vitro studies suggest that CC-115 is a sensitive CYP3A4 substrate. Co-administration of CC-115 with strong CYP3A4 inhibitors is predicted to increase the systemic exposure to CC-115; likewise CYP3A inducers can be expected to decrease systemic exposure to CC-115, possibly resulting in sub-therapeutic drug levels. Refer to Appendix C of master INSIGhT protocol for a list of prohibited drugs. Please note that this list may not be comprehensive.

3.5.2 Caution should be exercised when co-administering CC-115 with narrow therapeutic drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A. Participants receiving such medications must be monitored

for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate. Refer to Appendix C of master INSIGhT protocol for a list of drugs. Please note that this list may not be comprehensive

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

3.5.4 Corticosteroids should be used in the smallest possible dose to control symptoms of cerebral edema and mass effect, and discontinued if possible. Chronic dosing of corticosteroids is known to induce CYP3A enzymes, thereby increasing the risk of reducing CC-115 drug exposure to sub-therapeutic levels.

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

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

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

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

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

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

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

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

.5.12 Other anticancer or experimental therapies: No other anticancer therapy of any

kind is permitted during the study treatment period. No other drug under investigation may be used concomitantly with the study drug.

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

3.5.14 CC-115 related mucositis and mouth ulcers should be treated as early as possible and according to institutional standard medical practice. This may include analgesics, topical preparations (suspensions, pastes), and short courses of systemic steroids with temporary dose interruption and/or dose reduction for more severe cases. Alcohol or peroxide-containing mouthwashes should be avoided.

3.5.15 Acute renal insufficiency has been reported with mTOR pathway inhibitors. Typically this has been associated with drug-related gastrointestinal toxicities (anorexia, nausea, vomiting, diarrhea, mucositis) leading to dehydration and electrolyte abnormalities. Subjects should be monitored closely for these toxicities and treated with rehydration, antiemetics, and antidiarrheals as medically indicated. CC-115 dose interruption or modification may be indicated to manage these toxicities.

3.5.16 Infections (including the SAEs of pneumonia, sepsis, and nonserious AEs of infection) and associated pyrexia were reported with CC-115. Vigilance for the signs and symptoms of infection should be practiced with subjects receiving treatment with CC-115 and managed according to institutional standard medical practice. Routine infectious disease prophylaxis is not recommended; however, antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the investigator.

3.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue on the CC-115 arm until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

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

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Patrick Y. Wen, MD, at 617-632-2166 or pwen@partners.org.

3.7 Duration of Follow Up

Participants will be followed until death with monthly visits, telephone contact, or medical record review. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Refer to section 7 study calendar within this appendix for follow-up requirements and time points.

3.8 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

4. DOSING DELAYS/DOSE MODIFICATIONS

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug. If administration of CC-115 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in this section.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

All participants will be initially treated at Dose Level 0.

Table: CC-115 Dose Levels

Dose Level	Dose of CC-115
0 (starting dose)	10 mg every 12 hours
-1	7.5 mg every 12 hours
-2	5 mg every 12 hours

4.1 Anticipated Toxicities

In order for an event to be considered expected (known correlation to study drug/treatment) for the purposes of adverse event reporting, the event must be:

- Included in this section for CC-115.
- Included in this section or included in the package insert or the informed consent document as a potential risk for radiation therapy.

NOTE: For events that are secondary to an event deemed expected with a study agent/modality (e.g. rectal pain or hypokalemia as a result of diarrhea or gait disturbance as a result of edema cerebral), please record as "possibly related to" and "expected with" the agent/modality.

4.1.1 Anticipated Toxicities for Radiation Therapy

A list of adverse events of all grades suspected to be radiation therapy treatment related, organized by CTCAE v4.03 category, includes:

- EAR AND LABYRINTH DISORDERS – external ear inflammation; other: dryness of ear canal; other: hardening of ear canal wax; external ear pain; other: hearing loss
- ENDOCRINE DISORDERS - other: hypophysitis, or hypopituitarism
- EYE DISORDERS – cataract; other: decreased vision
- GASTROINTESTINAL DISORDERS – nausea; vomiting
- GENERAL DISORDERS – fatigue
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – dermatitis radiation; injury other: optic nerve
- INVESTIGATIONS –lymphocyte count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED – treatment related secondary malignancy
- NERVOUS SYSTEM DISORDERS – headache; seizure; memory impairment; cognitive disturbance; somnolence; dysgeusia; central nervous system necrosis; edema cerebral; other: tumor inflammation**
- PSYCHIATRIC DISORDERS – personality change
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – scalp pain; other: scalp redness; alopecia

4.1.2 Suspected & Anticipated Toxicities for CC-115

A list of adverse events of all grades suspected to be CC-115 treatment related according to review of Investigator's Brochure, experience with other drugs in the same class and preclinical data, organized by CTCAE v4.03 category, includes:

- BLOOD & LYMPHATIC SYSTEM DISORDERS – white blood cell decreased; platelet count decreased; anemia; lymphocyte count decreased
- GASTROINTESTINAL –diarrhea; nausea; vomiting; mucositis oral
- GENERAL DISORDERS- fatigue; fever
- INFECTIONS & INFESTATIONS –infection***; sepsis
- INVESTIGATIONS – creatinine increased; weight loss; aspartate aminotransferase increased; alanine aminotransferase
- METABOLISM & NUTRITION DISORDERS – anorexia; dehydration; hyperglycemia; hyponatremia; cholesterol high; hypertriglyceridemia,
- RENAL AND URINARY DISORDERS – acute kidney injury
- RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS – pneumonitis; hypoxia; pleural effusion; cough; dyspnea; respiratory failure
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS –rash acneiform; rash maculopapular; photosensitivity
- VASCULAR DISORDERS – thromboembolic events

* "Generalized muscle weakness" to also include other CTCAE terms inclusive of a muscle weakness

** As CTCAE v. 4 recognizes 'Edema cerebral' only as a Gr4 event, please record events of 'Edema cerebral' deemed by Investigator to be Gr1-Gr3 or Gr5 as 'Nervous system disorders, Other: Tumor inflammation' (Gr1-Gr3 or Gr5, accordingly).

*** General term "infection" to include all CTCAE infections

4.2 Dose Modifications/Delays for CC-115

4.2.1 Table 4.2 should be adhered to for all toxicities considered at least possibly related to CC-115. If a participant experiences a toxicity unlikely or unrelated to treatment with CC-115, but may still warrant a hold or reduction of study drug for safety, discussion and approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD, is strongly recommended.

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

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

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

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

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

4.2.5 No more than 1 levels of dose reduction are permitted in this study. Participants cannot be treated below dose level -2. If a participant whose CC-115 dose has been reduced by 1 dose levels requires another dose reduction, treatment on study must be stopped unless the participant has benefited from the study, in which case the investigator will contact the overall Principal Investigator, Dr. Patrick Y. Wen, to determine if the participant will remain in the study.

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

4.2.6.1 NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

4.2.7 Dose re-escalation (after dose reduction for toxicity) will only be permitted if a participant (including safety lead-in participants) is dose reduced during the initial 10 weeks of treatment (DLT period), then the dose of CC-115 may be escalated at the start of adjuvant Cycle 1 to dose level 0 if the treating investigator determines that it is in the best interest of the participant. Otherwise, no dose re-escalation is permitted on study.

4.2.8 **Cycle length will be 4 weeks (28 days), even if treatment is held for toxicity.** There isno stopping in counting cycles/days for those periods where a subject's drug is withheld.All study evaluations and treatments should continue as if study treatment is not being held.

4.2.9 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 4.2, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of CC-115. All SAEs must be reported as detailed in section 5.3 of this appendix.

Table 4.2: Criteria for dose-modification and re-initiation of CC-115 treatment

Table 4.2 should be adhered to for all toxicities attributable (considered at least possibly related) to CC-115 as noted below. If a participant experiences a toxicity unlikely or unrelated to treatment with CC-115 but may still warrant a hold or reduction of study drug for safety, discussion and written approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Toxicity (organized by CTCAE v 4.03)	**Actions**
Investigations (for hyperglycemia, see *Metabolism disorders*)	
ALT/SGPT or AST/SGOT **- Grade 2 (>3.0- 5.0 x ULN)**	First Occurrence: Interrupt until resolution to ≤ grade 1, then • If resolution to grade ≤1 in ≤ 10 days, resume CC-115 at the current dose level • If resolution to ≤ grade 1 takes > 10 days, resume CC-115 at one lower dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level
ALT/SGPT or AST/SGOT **- Grade 3** **(> 5.0 - 20.0 x ULN)**	First Occurrence: Interrupt until resolution to ≤ grade 1, then • If resolution to grade ≤1 in ≤ 10 days, resume CC-115 at the current dose level • If resolution to ≤ grade 1 takes > 10 days, resume CC-115 at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication. Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level. Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication.
ALT/SGPT or AST/SGOT **- Grade 4 (>20.0 x ULN)**	Interrupt CC-115 until resolution to ≤ grade 1, then resume CC-115 at one lower dose level Once resolved to ≤ grade 1, monitor liver function tests every other week or more frequently if clinically indicated until the end of treatment with study medication.
Amylase, asymptomatic **- Grade 3 (> 2.0 - 5.0 x ULN)**	First Occurrence: Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1in ≤ 10days, resume CC-115 at the current dose level; • If resolution to grade ≤1 in > 10days, resume CC-115 at one lower dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level

Amylase **- Grade 4 (> 5.0 x ULN)**	Discontinue CC-115
Bilirubin (for patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated	
Bilirubin* **- Grade 2 (>1.5 - 3 x ULN)**	First Occurrence: Interrupt CC-115 until resolution to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 10days, resume CC-115 at the current dose level; • If resolution to ≤ grade 1 takes > 10days, resume CC-115 at one lower dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level
Bilirubin* **- Grade 3** **(> 3.0 – 10.0 x ULN)**	Interrupt CC-115 until resolution to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 10days, resume CC-115 at one lower dose level; • If resolution to ≤ grade 1 takes > 10days, discontinue CC-115
Bilirubin **- Grade 4 (> 10.0 x ULN)**	Discontinue CC-115
* For participants with Gilbert's syndrome prior to registration, the clinician may choose to continue CC-115 for elevations in total bilirubin that are two times the participant's baseline value (screening value). For total bilirubin that is greater than two times the baseline value, follow dose modification guidelines as outlined in the above table. However, in place of resolution to ≤ grade 1, CC-115 may resume once resolution to ≤ 2 x baseline value.	
Cholesterol high and/or hypertriglyceridemia **-Grade 2**	Maintain dose if tolerable; recommend initiating treatment
Cholesterol high and/or hypertriglyceridemia **-Grade 3**	Omit dose of CC-115 and initiate treatment until resolved to ≤ grade 1, then restart at one lower dose level.
Cholesterol high and/or hypertriglyceridemia **-Grade 4**	Discontinue CC-115
Creatinine **- Grade 2 (>1.5 - 3 x ULN)**	First Occurrence: Interrupt treatment until resolution to ≤ grade 1, then • If resolved to ≤ grade 1 in ≤ 10days, resume CC-115 at the current dose level • If resolution to ≤ grade 1 takes > 10days, resume CC-115 decreased by one dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level
Creatinine **- Grade 3 (> 3.0 - 6.0 x ULN)** **- Grade 4 (> 6.0 x ULN)**	Discontinue CC-115
Lipase elevation, asymptomatic **- Grade 3 (> 2.0 - 5.0 x ULN)**	First Occurrence: Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 10 days, resume CC-115 at the current dose level; • If resolution to grade ≤1 in > 10 days, resume CC-115 at one lower dose level Second/Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level

Lipase elevation, asymptomatic **- Grade 4 (> 5.0 x ULN)**	Discontinue CC-115
Neutropenia **- Grade 3** **- (ANC 0.5 - 0.9 x 109/L)Grade 4** **(ANC < 0.5 x 10^9/L)** (see *Blood Disorders* for Febrile Neutropenia)	<u>First Occurrence:</u> Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 7 days, then resume CC-115 at the current dose level • If resolution to grade ≤1 in > 7 days, then resume CC-115 at one lower dose level <u>Second/Third Occurrence:</u> Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level
Thrombocytopenia **- Grade 3** **(PLT 25-49 x 10^9/L)**	<u>First Occurrence:</u> Interrupt until resolved to ≤ grade 1, then: • If resolution to grade ≤1 in ≤ 14 days, resume CC-115 at the current dose level • If resolution to grade ≤1 in > 14 days, then resume CC-115 at one lower dose level <u>Second/Third Occurrence:</u> Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level
Thrombocytopenia **- Grade 4 (PLT < 25 x 10^9/L)**	Interrupt until resolved to ≤ grade 1, then resume CC-115 at one lower dose level
Blood and lymphatic system disorders	
Febrile neutropenia **- ANC < 1.0 x 10^9/L with a single temperature of > 38.3 °C (101 F) or a sustained temperature of ≥ 38°C (100.4 F) for more than one hour**	Interrupt treatment until resolved, then resume CC-115 at one lower dose level. Febrile neutropenia should be managed promptly with broad-spectrum antibacterial therapy, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. Anemia and thrombocytoenpia should be treated supportively and if necessary, with red cell or platelet transfusions.
Gastrointestinal Disorders	
Diarrhea **- Grade 2 (4-6 stools/day > pretx)**	Early treatment of diarrhea is recommended. Patients should be instructed to initiate anti-diarrheal therapy (such as loperamide) and notify the investigator at the first sign of loose stool. Investigators should assess the response of anti-diarrheal therapy within 24 hours of notification. If diarrhea can be controlled with optimal anti-diarrheal treatment within 48 hours to either baseline or grade 1, continue CC-115. If not, interrupt treatment until resolved to ≤ grade 1, then resume CC-115 at the current dose.
Diarrhea **- Grade 3 (≥7 stools/day > pretx)** **- Grade 4** **(urgent intervention indicated)**	Early treatment of diarrhea is recommended. Patients should be instructed to initiate anti-diarrheal therapy (such as loperamide) and notify the investigator at the first sign of loose stool. Investigators should assess the response of anti-diarrheal therapy within 24 hours of notification. If diarrhea can be controlled with optimal anti-diarrheal treatment within 48 hours to either baseline or grade 1, continue CC-115. If not, for diarrhea ≥ Grade 3, interrupt treatment until resolved to ≤ grade 1, then resume CC-115 at one lower dose level.

General Disorders	
Fatigue Grade 1 & 2	Maintain dose level. Initiating a stimulant agent is recommended.
Fatigue **- Grade 3**	First / Second Occurrence: Interrupt CC-115 until resolved to ≤ grade 1, then: • If resolved in ≤ 14 days, resume CC-115 at the current dose level • If resolved in > 14 days, resume CC-115 at one lower dose level Third Occurrence: Interrupt until resolution to ≤ grade 1, then resume CC-115 at one lower dose level
Metabolism and Nutrition disorders	
Hypercalcemia **Grade 1-3**	Management of hypercalcemia per local institutional guidelines. CC-115 administration will continue daily. For patients requiring hospitalization for management of hypercalcemia, CC-115 administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Hypercalcemia **Grade 4**	Management of hypercalcemia per local institutional guidelines. CC-115 administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Hyperuricemia **Grade 1-4**	Management of hyperuricemia per local institutional guidelines. CC-115 administration will continue daily. If grade 4 persists > 14 days despite medical management, CC-115 administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Hypophosphatemia **Grade 1-4**	Initiate phosphorous supplementation daily. CC-115 administration will continue daily. If grade 4 persists > 14 days despite medical management, CC-115 administration should be held until resolution to < grade 1 and resumed at one dose level lower.
Nervous system disorders	
Neurotoxicity ≥ 1 CTCAE grade level increase, attributable to drug	Maintain dose level
Neurotoxicity ≥ Grade 3, attributable to drug	Interrupt CC-115 until resolved to ≤ grade 1 or baseline, then resume CC-115 at one lower dose level
Skin and subcutaneous tissue disorders	
Any Rash **Grade 1**	Maintain dose level. Consider initiating appropriate skin toxicity therapy such as antihistamines.
Any Rash **Grade 2**	Maintain dose level. Initiate/intensify appropriate skin toxicity therapy such as antihistamines.
Any Rash **Grade 3**	Interrupt CC-115 until resolution to CTCAE Grade ≤ 1, then: • If resolved in ≤ 7 days, resume CC-115 at one lower dose level • If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue participant from study drug treatment.
Any Rash **Grade 4**	Discontinue CC-115

Other unspecified RELATED adverse events	
Other unspecified Grade 1 and 2 events considered at least possibly related to CC-115	Maintain treatment with CC-115
Other unspecified Grade 3 clinically significant events considered at least possibly related to CC-115	Interrupt treatment until resolution to ≤ grade 1 or returned to baseline, treatment may resume at the same dose level or a 1 dose level decrease, at the investigator's discretion. Continuation of CC-115 is permitted upon recovery to stable Grade 2 if the investigator and overall principal investigator (Dr. Patrick Y. Wen) agree that the event is not considered clinically significant.
Other unspecified Grade 4 events considered at least possibly related to CC-115	Discontinue CC-115

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (section 4.1 of this appendix) and the characteristics of an observed AE (section 5.2 of this appendix) will determine whether the event requires expedited reporting **in addition** to routine reporting.

This section specifies reporting requirements to the FDA, Overall PI/Coordinating Center, DF/HCC IRB, and manufacturer as applicable.

5.1 Expected Toxicities

Refer to section 4.1 of this appendix for expected toxicities for assigned study treatment arm.

5.2 Adverse Event Characteristics

- **Adverse Event (AE) Definition:**
  An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

  Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study

medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized or determined to be irreversible by an investigator.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in section 4.1 of this appendix should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

- **Serious Adverse Event (SAE) Definition**:
  A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:
    - Results in death
    - Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
    - Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
    - Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
    - Is a congenital anomaly/birth defect;
    - Constitutes an important medical event. Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

5.3 Expedited Adverse Event Reporting

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

5.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event that is *Serious, Unexpected,* and there is a *Reasonable Possibility* (i.e., possible, probable, or definitive attribution) the Adverse Event is related to the study intervention.

5.3.3 **Expedited Reporting Guidelines to Overall PI/Coordinating Center & Celgene**

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites outside of DF/HCC will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the AE form should be forwarded to the Overall PI within the timeframes detailed in the table below. The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to the DFCI IRB policies and procedures in reporting adverse events.

In addition to local IRB reporting policies, all sites are required to follow the Table 5.3.3 expedited reportable AE requirements:

NOTE: Until patients initiate treatment with CC-115 on study, please report per Table 5.3.3 'Expedited AE Reporting by external sites to Coordinating Center/Overall PI' of Appendix E (Control Arm).

Table 5.3.3 Expedited AE Reporting Requirements to Celgene & DFCI Coordinating Center

Adverse Event Characteristics				Reporting Requirement	
Seriousness	**Toxicity**	**Known Correlation[f]**	**Attribution to CC-115**	**Celgene Corp - Via Fax or email[c] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**	**Overall PI (Patrick Y. Wen, MD) at the DFCI Coordinating Center Via Email [b] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**
Serious[e]	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [a]	Within 24 hours from notification [a]
Non-Serious	Grade 4	Any (Expected or Unexpected)	Any	Not Required	Within 5 working days from notification [a]
Non-Serious	Grade 2 or 3	Unexpected	Possible, probable, definite	Not Required	Within 7 working days from notification [a]

a. In the event that the participating investigator/site team does not become aware of an adverse event requiring expedited reporting immediately (e.g., participant sought treatment elsewhere), the participating investigator/site team is to report the event within the required hours/days noted above after learning of it and document the time of his or her first awareness of the adverse event. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE or reportable AE is required.

b. Email the Medwatch 3500A form, reportable AE coversheet (section 10 of this appendix), and the local IRB SAE report (if applicable) to the DFCI Coordinating Center with the subject title as "INSIGHT SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Patrick Y. Wen, and to the DFCI Coordinating Center personnel.

c. Reportable AE Coversheet is found in section 10 of this appendix. The coversheet contains all FAX numbers/e-mails and needed for reporting purposes.

d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm

e. Seriousness is defined in section 5.2 of this appendix.

f. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Anticipated Toxicities list (protocol section 4.1 of this appendix) which is derived from the Investigator's Brochure.

5.3.4 How to report expedited AEs to Celgene & DFCI Coordinating Center/Overall PI

3. Document/describe reportable AE(s) on the following:
    a. MedWatch 3500A
        i. downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. DFCI Reportable AE Coversheet – INSIGhT CC-115 Arm
        i. Coversheet can be found in section 10 of this appendix. The coversheet contains contact information for DFCI Coordinating Center and Celgene safety groups. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.
4. Scan and email above documents to NeuroOnc_SAE@dfci.harvard.edu with the subject title "INSIGHT SAE"
    a. All AE reports received at this account are forwarded immediately to Overall Principal Investigator (Dr. Patrick Y. Wen), and to Coordinating Center personnel.
    b. If available and applicable, also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.

5.3.5 Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

- Lymphopenia (grades 2-3). **NOTE: all grade 4 lymphopenia events should be reported per expedited adverse event reporting requirements to the DFCI Coordinating Center**
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for treatment of patient's underlying disease after coming off study treatment (e.g. admission after patient is removed from active study treatment for craniotomy)

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

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

5.5 Expedited Reporting to Hospital Risk Management

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

5.6 Routine Adverse Event Reporting

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

5.7 Other Reporting Requirements

5.7.1 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) in either a female subject or a partner of a male subject occurring while the subject is on investigational product (IP), or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the subject instructed to return any unused CC-115. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form.

The female may be referred to her obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form as a follow-up to the initial pregnancy report.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus must be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

5.7.2 Overdose

Overdose, as defined for this protocol, refers to CC-115 dosing only.

On a per dose basis, an overdose is defined as a dose of CC-115 at any amount over the protocol-specified dose assigned to a given patient, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Notify the DFCI Coordinating Center at NeuroOnc_SAE@dfci.harvard.edu of any potential overdose as soon as possible.

5.7.3 IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows:

Celgene Corporation
Attn: Medical Affairs Operations
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

6. PHARMACEUTICAL INFORMATION

CC-115

6.1.1 Description

The chemical name for CC-115 is 1-ethyl-7-(2-methyl-6-(4H-1,2,4-triazol-3-yl)pyridin-3-yl)-3,4-dihydropyrazino[2,3-b]pyrazin-2(1H)-one. CC-115 is also known as CC0483115 and has an empirical formula of C16H16N8O and a molecular weight of 336.35.

In vitro metabolism studies demonstrated that CC-115 is subject to metabolism via multiple pathways: oxidative metabolism primarily catalyzed by CYP3A4 and CYP2C8 (and to a minor extent by CYP1A2, CYP2C19 and CYP2D6), and direct glucuronidation by UGT1A1. The relative contribution of each of these enzymes to the overall in vivo clearance of CC-115 is not known at this time. Therefore, caution should be exercised when CC-115 is co-administered with potent CYP3A4 inhibitors (eg, ketoconazole, ritonavir, grapefruit juice, clarithromycin), CYP2C8 inhibitors (eg, montelukast, gemfibrozil, trimethoprim), and CYP2C8/3A4 inducers (eg, rifampicin, phenytoin, carbamezepine, phenobarbital). Since CC-115 is subject to glucuronidation by UGT1A1, exercise caution also when treating subjects with Crigler-Najjar and Gilbert's syndromes.

The metabolite M2 (keto-CC-115) was the predominant circulating human metabolite constituting approximately 20% of drug-related component, and this M2 metabolite has demonstrated minimal pharmacological activity towards the mTOR target.

In humans, CC-115 is rapidly absorbed with mean peak plasma levels generally observed between 30 minutes and 3 hours after single and multiple oral doses of CC-115. The range of geometric mean terminal half-life of CC-115 is approximately 4 to 8 hours after single dose administration. Following single and multiple once-daily administration of CC-115, mean CC-115 exposure (AUC_{24}, AUCt, and Cmax) increased in an approximate linear, dose-proportional manner over the 4- to 40-mg dose range.
CC-115 accumulation in plasma was minimal to moderate with exposure generally increasing from approximately 20% to 60% based on overall CC-115 exposure (ratio of geometric mean AUC_{24} Day 15/Day 1) after repeated once-daily and twice-daily administration of CC-115. Renal clearance of CC-115 was negligible and only a small fraction of the CC-115 dose (< 1%) was excreted as unchanged CC-115 in urine.

In vitro CYP inhibition studies demonstrated that CC-115 produced no or only weak inhibition of CYP and no induction of CYP; thus, CC-115 is not expected to precipitate clinically relevant drug-drug interactions due to CYP interactions. CC-115 is not a substrate but is an inhibitor of human P-gp. CC-115 is a substrate and an inhibitor of human BCRP. Therefore, it is recommended that caution be exercised when CC-115 is coadministered with P-gp substrates (eg, digoxin and new oral anticoagulants), BCRP substrates (eg, topotecan), and BCRP inhibitors.

6.1.2 **Form**

CC-115 drug is manufactured and supplied by the Celgene Corporation. The formulation of CC-115 to be administered in the clinical studies is a reddish brown hard gelatin capsule in the appropriate strengths (10mg, 5mg and 7.5mg), containing only the active pharmaceutical ingredient. No other excipients are used in the product capsules.

Both the CC-115 capsules are packaged in high-density polyethylene bottles fitted with induction seals and child-resistant polypropylene closures.

6.1.3 **Storage and Stability**

Store as directed on the label.

6.1.4 **Compatibility**

There are no known compatibility issues.

6.1.5 **Handling**

Routine chemotherapy handling is recommended.

6.1.6 **Availability**

CC-115 is an investigation agent and will be supplied free-of-charge from Celgene Corporation.

6.1.7 **Preparation**

None.

6.1.8 **Administration**

- CC-115 will be administered at a starting dose of 10 mg every 12 hours. Participants should be instructed to take their doses, twice a day, at approximately the same times each day and approximately 12 ± 3 hours apart.
- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.
- If the participant forgets to take a CC-115 dose more than 3 hours from the intended time, then that dose should be withheld and CC-115 should be restarted at the time of the next planned dose.

6.1.9 **Ordering**

The agent will be ordered from each institution's individual pharmacy (or designee) using a Celgene Corporation online drug ordering system. Access to this system will be requested for each institution's pharmacy by the DFCI Coordinating Center once local IRB approval is received. Anticipate 3-5 business days to receive drug after the order is placed.

6.1.10 **Accountability**

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

6.1.11 **Destruction and Return**

CC-115 will be destroyed on site according to institutional policies, documented in the Drug Accountability Record Form. At the time of expiration / study close, a drug disposition form provided by Celgene Corporation will be sent out to be signed off by the Pharmacist and Investigator verifying the destruction of drug. At the end of the study, unused supplies of CC-115 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7. STUDY CALENDAR

Assessment	Screen-ing[a]	Initiation Cycle									Adjuvant Cycles	End of Tx[g]	30-Day Post Drug[h]	Active Follow-Up[i]	Long Term Follow-Up[j]
		D1[b]	D8[c,e]	D15[c,e]	D22[c]	D29[c,e]	D36[c,e]	D43-49[d]	D57[c,e]	D64[c,e]	D1[f]				
Informed Consent[k]	X														
Medical History[l]	X														
Inclusion/Exclusion Criteria[m]	X														
Vital signs[n]	X	X	X	X	X	X	X	X	X	X	X	X			
Physical Exam	X	X			X			X			X	X			
Neurologic Exam	X	X			X			X			X	X			
Karnofsky Performance Status[o]	X	X			X			X			X	X			
Concomitant Medications[p]	----------X----------														
Adverse Events[q]		----------X----------													
Pregnancy Test (β-HCG)[r]	X	X			X						X	X			
Coagulation[s]	X														
Hematology[t]	X	X	X	X	X	X	X	X	X	X	X	X			
8-hour Fasting Serum Chemistry[u]	X	X	X	X	X	X	X	X	X	X	X	X			
HbA1c[bb]		X						X			X	X			
8 –hour Fasting Lipid Profile		X						X			X	X			
12-lead ECG[v]	X	X[v]		X[v]		X[v]					X[v]				
Radiation[w]		----------X----------													
CC-115		----------X----------													
Imaging – MRI[x]	X	X									X	X		X	
Response Assessment[y]											X	X		X	
Post-treatment therapies[z]														X	X
Survival[aa]														X	X

a. All screening procedures to be performed within 28 days of initial registration. **NOTE: refer to section 10 of master protocol for comprehensive details on screening assessments, initial registration, randomization assignment and second registration timing.**

b. Concomitant radiation and CC-115 must begin no later than 42 days following initial surgery. Day 1 assessments must be performed within 3 days of starting study treatment. Screening assessments may be utilized as baseline/Day 1 assessments if they fall within window.

c. +/- 2 day window for weekly assessments during concomitant phase.

d. Day 43-49 visit to occur within +/- 7 days of completing radiation.

e. Clinic Visits required for Safety Lead-In patients only (weekly AE assessments for 10-week DLT period); non-Safety Lead-In patients may have these assessments performed locally.

f. Adjuvant C1D1 to begin >28 (+14) days following end of radiation. Cycle 1, Day 1 adjuvant assessments to be performed within 4 days of Day 1 CC-115. All adjuvant cycle 1, day 1 assessments must be resulted and reviewed prior to initiating treatment with CC-115. **Adjuvant cycles will be 28 days even if treatment is held**. Day 1 assessments for

subsequent adjuvant cycles to be performed within 4 days prior to Day 1 CC-115. (If utilizing the assessment window, that does *not* shorten the previous cycle or extend the upcoming cycle; each = 28 days.)

g. End of Treatment: assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment.
h. 30-Day Post Drug: a contact/visit is to be performed 30 days (+7 days) after date of last drug taken on study. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last drug.
i. Active Follow-Up: participants who discontinue study treatment for reasons other than disease progression will be followed every 4 weeks (+/-1 week) via contact or medical record review andstudy team must continue monitoring participant's disease status by radiologic imaging at 8-week intervals (+/- 1 week) until (1) documented disease progression, (2), death, (3) participant withdraws from follow-up, or (4) end of study, whichever occurs first.
j. Long Term Follow-Up: participants will be followed every 4 weeks (+/-1 week) via contact or medical record review until death. Participants must be followed for survival data at every long-term follow-up time point and for post-treatment therapies and reason for stopping those therapies when available.
k. Informed Consent: must be obtained by MD attending. No study specific screening procedures may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration. Following initial registration and receipt of INSIGhT randomization assignment, participants must be sign the consent form specific to the assigned treatment arm prior to initiating treatment for that study arm.
l. Medical History: to include review of treatment history for GBM, any ongoing medical conditions & medical history pertaining to eligibility on study and involvement during study.
m. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements for initial registration. See section 2 of this appendix for arm specific eligibility criteria.
n. Vital Signs: weight, heart rate, blood pressure, respiration rate, temperature. Vital signs must be performed prior to administration of treatment on treatment days. Height required only at screening.
o. Karnofsky Performance Status (KPS): see appendix A of master protocol.
p. Concomitant Medications: concomitant medications & reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.
q. Adverse Events: adverse events experienced by participants will be collected and recorded from the first dose of treatment on-study up to the 30-Day Post Drug Visit of the last dose of study medication (+ 7 days depending on when 30-Day Post Drug visit/contact occurs).
r. Pregnancy Test: required for women of child bearing potential (see section 3 of master protocol for definition of women of child bearing potential).
s. Coagulation: PT/INR, PT, PTT required at screening only.
t. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
u. 8-hour Fasting Serum Chemistry: albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed), amylase, lipase, and magnesium.
v. 12-Lead ECG: required at screening, concomitant day 1 pre-dose and 1.5 hours (+/- 30 minutes) after dosing, concomitant day 15 1.5 hours (+/- 30 minutes) after dosing, and concomitant 29 1.5 hours (+/- 30 minutes) after dosing. 12-Lead ECGs will then be required concurrently with adjuvant cycles that require radiographic disease assessments (i.e., C1, C3, C5, etc.) at 1.5 hours (+/- 30 minutes) after dosing unless clinically significant abnormalities have been detected. No ECGs are required beyond adjuvant Cycle 5 unless clinically indicated.
w. Radiation: see section 3.1 of this sub-study appendix for definition of standard radiation therapy per protocol.
x. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site, Appendix D Recommended MRI Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial. Local reading (investigator assessment) will be used to determine eligibility and for participant management. Adjuvant C1D1 imaging should be performed within 7 days prior to starting adjuvant treatment; subsequent imaging should be performed within 7 days prior to Day 1 of odd cycles.
y. Response Assessment: Per RANO criteria (see section 11 of master protocol).
z. Post-treatment Therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected when available.
aa. Survival: date of death and reason must be collected for overall survival purposes.
bb. HbA1c & 8-hour fasting lipid profile: do not need to be resulted and reviewed prior to initiating CC-115 with RT in the concomitant phase.

8. MEASUREMENT OF EFFECT

Refer to section 11 of master INSIGhT protocol for details on measurement of effect.

9. REFERENCES

Mortensen DS, Perrin-Ninkovic SM, Shevlin G, Elsner J, Zhao J, Whitefield B, et al. Optimization of a Series of Triazole Containing Mammalian Target of Rapamycin (mTOR) Kinase Inhibitors and the Discovery of CC-115. J Med Chem. 2015 Jul 23;58(14):5599-608.

Fruman, D. A.; Rommel, C. PI3K and cancer: lessons, challenges and opportunities. Nat. Rev. Drug Discovery 2014, 13, 140−156.

Engelman JA. Targeting PI3K signaling in cancer: opportunities, challenges and limitations. Nat Rev Cancer 2009;9(8):550-62.

Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. Cell 2013; 155: 462-77.

Collis SJ, DeWeese TL, Jeggo PA, Parker AR. The life and death of DNA-PK. Oncogene 2005;24:949-961.

Bozulic L, Surucu B, Hynx D, Hemmings BA. PKBα/Akt1 acts downstream of DNA-PK in the DNA double-strand break response and promotes survival. Mol Cell 2008;30:203-213.

Surucu B, Bozulic L, Hynx D, Parcellier A, Hemmings BA. In vivo analysis of protein kinase B (PKB)/Akt Regulation in DNA-PKcs-null mice reveals a role for PKB/Akt in DNA damage response and tumorigenesis. J Biol Chem 2008;283:30025–30033.

Khanna KK, Jackson SP. DNA double-strand breaks: signaling, repair, and the cancer connection. Nature Genetics 2001; 27: 247-254.

Zhao Y, Thomas HD, Batey MA, Cowell IG, Richardson CJ, Griffin RJ, et al. Preclinical evaluation of a potent novel DNA-dependent protein kinase inhibitor NU7441. Cancer Res 2006;66:5353-5362.

Sarkaria JN, Galanis E, Wu W, et al. North Central Cancer Treatment Group Phase I Trial N057K Of Everolimus (RAD001) And Temozolomide In Combination With Radiation Therapy In Patients With Newly Diagnosed Glioblastoma Multiforme. Int. J. Radiation Oncology Biol. Phys., 2011;81:468–475.

DFCI REPORTABLE AE COVERSHEET – INSIGHT CC-115 ARM

DF/HCC Protocol No. 16-443 **Celgene Tracking No.** CC-115-CL-GBM-PI-007141

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this AE):

☐ Dr. Patrick Y. Wen and Dana-Farber Coordinating Center
Email: NeuroOnc_SAE@dfci.harvard.edu

☐ Celgene Corporation Fax: 908-673-9115 Email: drugsafety@celgene.com

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

Participant # and Initials:	
Date Event Met Reporting Criteria (as defined in protocol):	
Type of Report: ☐Initial ☐Follow-up	Hospitalization? ☐ Yes ☐ No

CTCAE Event #1 Description:	CTCAE Event #2 Description (if applicable)*:* *NOTE: use another coversheet if more than 2 events are being reported at this time*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death
Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness to **CC-115**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **CC-115**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **CC-115**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **CC-155**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Reporting Investigator (print):	

Signature of Reporting Investigator:_____Date:_____

RADIATION CC-115 DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Month & Year:_____CC-115 Dose:_____mg, two times a day.

TAKE_____pill(s) in the morning and_____pill(s) in the evening.

CC-115 Description:

- Your study drug (CC-115) is supplied as a 5mg, 7.5mg or 10mg reddish brown capsule

CC-115 Instructions – When and How:

- Take study drug (CC-115) twice a day, once in the morning and once in the evening.
- Take the drugs at approximately the same time each morning and evening, so that you are taking the drugs around 12 hours apart.
- Take the pill(s) with a glass of water and swallow them whole; do not chew them or crush them.
- Do not skip any doses.
- If you forget to take your pills in the morning you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time in the evening (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you forget to take your pills in the evening, you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time the next morning (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you vomit your pills, write this down in your pill diary. Do not take a replacement dose. Take the next scheduled dose as usual (one dose only). Please call your study nurse or doctor to discuss vomited doses.

Additional Instructions:

- You must avoid eating or drinking any foods with Seville oranges (like marmalade), grapefruit or foods or drink with grapefruit, and any exotic fruits during the entire treatment period.
- Keep your study drug in the original container(s) at room temperature. Keep study drug away from children, persons cannot read the label, and pets.
- Do not throw away empty bottles, and do not throw the study drug in the trash or flush into the toilet.
- Bring this diary, all pill bottles, and any unused pills to each clinic visit. Your Treatment Team will collect your diary, all pill bottles and any unused study drug, and you will be given a new pill diary at that time.
- Contact your study doctor or nurse if you are having any new or worsening side effects.
- Do not begin any new medication, over-the-counter drug, or herbal preparation without first checking with your Treatment Team to determine if it is acceptable to take while on this study.
- CC-115 absorbs ultraviolet (UV) light. It is not yet known if CC-115 may make your skin or eyes more sensitive to sunlight. As a precaution, it is advised you avoid prolonged exposure to natural or artificial sunlight (UVA/B) while taking CC-115 by wearing sun-protective clothes, applying effective sun block to exposed skin, and by wearing UV protective sunglasses.

To be completed by study personnel: Patient ID #________Patient Initials:________Month & Year:___________CC-115 Dose:___________mg

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

To be completed by study personnel: Patient ID #________Patient Initials:________Month & Year:___________CC-115 Dose:___________mg

Day 22	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials
Day 29	**Day 30**	**Day 31**	**Day 32**	**Day 33**	**Day 34**	**Day 35**
Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials
Day 36	**Day 37**	**Day 38**	**Day 39**	**Day 40**	**Day 41**	**Day 42**
Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials	Date: A.M. DOSE No. of pills: ________ Time: ___________ P.M. DOSE No. of pills: ________ Time: ___________ __________ Initials

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____CC-115 Dose:_____mg

Day 43	Day 44	Day 45	Day 46	Day 47	Day 48	Day 49
Date: A.M. DOSE No. of pills: _____ Time: _____ P.M. DOSE No. of pills: _____ Time: _____ _____ Initials	Date: A.M. DOSE No. of pills: _____ Time: P.M. DOSE No. of pills: _____ Time: _____ _____ Initials	Date: A.M. DOSE No. of pills: _____ Time: _____ P.M. DOSE No. of pills: _____ Time: _____ Initials	Date: A.M. DOSE No. of pills: _____ Time: _____ P.M. DOSE No. of pills: _____ Time: _____ Initials	Date: A.M. DOSE No. of pills: _____ Time: _____ P.M. DOSE No. of pills: _____ Time: _____ Initials	Date: A.M. DOSE No. of pills: _____ Time: P.M. DOSE No. of pills: Time: _____ _____ Initials	Date: A.M. DOSE No. of pills: _____ Time: P.M. DOSE No. of pills: _____ Time: _____ _____ Initials

Participant/Guardian Signature:_____ Date: _____

To be completed by study personnel:

# of 5 mg Bottles Returned: _____ # of 5 mg Pills Returned: _____
# of 7.5 mg Bottles Returned: _____ # of 7.5 mg Pills Returned: _____
# of 10 mg Bottles Returned: _____ # of 10 mg Pills Returned: _____

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

POST RADIATION CC-115 DOSING INSTRUCTIONS & DRUG DIARY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Cycle #:_____Month & Year:_____CC-115 Dose:_____mg, two times a day.

TAKE_____pill(s) in the morning and_____pill(s) in the evening.

CC-115 Description:

- Your study drug (CC-115) is supplied as a 5mg, 7.5mg or 10mg reddish brown capsule

CC-115 Instructions – When and How:

- Take study drug (CC-115) twice a day, once in the morning and once in the evening.
- Take the drugs at approximately the same time each morning and evening, so that you are taking the drugs around 12 hours apart.
- Take the pill(s) with a glass of water and swallow them whole; do not chew them or crush them.
- Do not skip any doses.
- If you forget to take your pills in the morning you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time in the evening (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you forget to take your pills in the evening, you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time the next morning (one dose only). Please call your study nurse or doctor to discuss missed doses.
- If you vomit your pills, write this down in your pill diary. Do not take a replacement dose. Take the next scheduled dose as usual (one dose only). Please call your study nurse or doctor to discuss vomited doses.

Additional Instructions:

- You must avoid eating or drinking any foods with Seville oranges (like marmalade), grapefruit or foods or drink with grapefruit, and any exotic fruits during the entire treatment period.
- Keep your study drug in the original container(s) at room temperature. Keep study drug away from children, persons cannot read the label, and pets.
- Do not throw away empty bottles, and do not throw the study drug in the trash or flush into the toilet.
- Bring this diary, all pill bottles, and any unused pills to each clinic visit. Your Treatment Team will collect your diary, all pill bottles and any unused study drug, and you will be given a new pill diary at that time.
- Contact your study doctor or nurse if you are having any new or worsening side effects.
- Do not begin any new medication, over-the-counter drug, or herbal preparation without first checking with your Treatment Team to determine if it is acceptable to take while on this study.
- Each post-radiation cycle is 28 days of morning and evening pills. If you start the cycle in the evening (P.M. dose), you may end the cycle in the morning of the 29th day.
- CC-115 absorbs ultraviolet (UV) light. It is not yet known if CC-115 may make your skin or eyes more sensitive to sunlight. As a precaution, it is advised you avoid prolonged exposure to natural or artificial sunlight (UVA/B) while taking CC-115 by wearing sun-protective clothes, applying effective sun block to exposed skin, and by wearing UV protective sunglasses.

To be completed by study personnel: Patient ID #________ Patient Initials:________ Month & Year:___________ CC-115 Dose:___________mg

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

Participant/Guardian Signature:___________________________________ **Date:** ________________

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____CC-115 Dose:_____mg

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

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

Participant/Guardian Signature: _____ Date: _____

To be completed by study personnel:

# of 5 mg Bottles Returned: _____ # of 5 mg Pills Returned: _____
# of 7.5 mg Bottles Returned: _____ # of 7.5 mg Pills Returned: _____
# of 10 mg Bottles Returned: _____ # of 10 mg Pills Returned: _____

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

APPENDIX H NERATINIB ARM OF INSIGHT

TABLE OF CONTENTS

1. BACKGROUND

1.1 Temozolomide

Background and preclinical data
Temozolomide is a member of the imidazotetrazine family that is structurally related to the alkylating agent dacarbazine and has shown efficacy against a variety of cancers, including high grade gliomas.

Under physiologic conditions, temozolomide is spontaneously converted to its active metabolite MTIC (5-(3-dimethyl-1-triazenyl)imidazole-4-carboxamide)[1]. The breakdown product of MTIC, methyldiazonium, is an actively alkylating agent that preferentially methylates guanine residues of the DNA molecule, thereby resulting in single and double DNA strand breaks and activation of apoptotic pathways.[2] Temozolomide has linear and reproducible pharmacokinetics with 100% p.o. bioavailability within 2 hours of drug administration and a rapid plasma drug clearance with a plasma half- life of 1.6-1.8 hours.[3]

Because of its lipophilic properties, temozolomide penetrates into the central nervous system (CNS) and was shown to reach acceptable CNS concentrations. In humans, the CSF penetration is estimated to be ~20-30% based on AUC_{plasma}/AUC_{CSF} ratios.[4] In several preclinical rodent and primate models, it was demonstrated to have activity against CNS tumors thereby stimulating interest for investigations in humans.[5-8]

Clinical data
In these preclinical and clinical phase I studies, temozolomide demonstrated antitumor-activity in high-grade gliomas in adults.[3,9] Based on these studies, the maximal tolerated dose (MTD) for humans has been defined as 150-200 mg/m2 per day depending on whether patients have received prior treatment with myelotoxic agensts.[3,10,11] For patients with glioblastoma, the recommended temozolomide doses are 75 mg/m2 during radiation (concomitant phase) and 150-200 mg/m2 for 5 days out of a 28-day cycle for 6 months.[4,12] Temozolomide in general is well tolerated and the most frequent toxicities are mild to moderate myelosuppression (thrombocytopenia and neutropenia) which is predictable and typically resolves spontaneously.

Subsequent phase II studies confirmed the activity of temozolomide against newly diagnosed and recurrent high-grade gliomas[1,13,14] therefore leading to further evaluation of the drug by the European Organization for Research and treatment of Cancer (EORTC) and the National Cancer Institute of Cancada (NCIC) in a landmark phase III study[15]. In this clinical trial the efficacy of radiation with concomitant temozolomide followed by six monthly cycles of temozolomide compared to radiation alone for newly diagnosed glioblastoma was evaluated[15]. The combination of radiation and temozolomide prolonged median progression free survival from 5 to 6.9 months (95% CI 4.2-5.5) and median overall survival from 12.1 to 14.6 months (95% CI 11.2-13.0). Treatment with temozolomide was overall well tolerated with grade 3 or 4 hematoxicity in 16% of study participants.

Based on these results, this concomitant use of temozolomide during radiation followed by monthly maintenance cycles has been widely accepted as the standard of care treatment for patients with newly diagnosed glioblastoma.

MGMT

The tumor suppressor gene MGMT (O^6-methylguanine-DNA methyltransferase) on chromosome 10q26 encodes a DNA-repair enzyme that removes alkyl groups from the O^6 position of guanine, thereby repairing the lethal DNA-cross links induced by alkylating chemotherapeutic agents such as temozolomide[16]. Glioma cells with diminished MGMT activity are more responsive to the alkylating damage of these agents[17,18]. Epigenetic silencing of the MGMT promoter is present in ~40-68% of high grade gliomas and leads to reduced protein expression and cellular DNA repair activity. MGMT promoter methylation is associated with longer survival in patients with high grade gliomas treated with alkylating agents[19], including temozolomide[20,21] Therefore, MGMT promoter methylation represents a favorable prognostic marker for high grade gliomas which is routinely evaluated in neuropathological practice.

In a retrospective tumor tissue analysis of the patients enrolled in the EORTC/NCIC study, MGMT promoter methylation was confirmed to be a favorable prognostic factor for patients with glioblastoma.[21] It also showed that the therapeutic benefit of temozolomide in addition to radiation was most pronounced in patients whose tumors contained a methylated MGMT promoter. In this patient group, combined chemoradiation compared to radiation alone prolonged progression-free survival from 5.9 (95% CI 5.3-7.7) to 10.3 (95% CI 6.5-14.0) months and median overall survival from 15.3 (95% CI 13.0-20.9) to 21.7 (95% CI 17.4-30.4) months. In contrast, for patients without MGMT promoter methylation the combination of temozolomide plus radiation resulted in an only small survival benefit compared to radiation alone (progression free survival 4.4 vs, 5.3 months, overall survival 11.8 vs. 12.7 months).

Rationale

These data suggest a correlation between MGMT promoter methylation and treatment response to temozolomide. It therefore can be argued that temozolomide is useful only in the MGMT methylated setting. However, based on the small subgroup of study patients from the landmark EORTC-NCIC study whose tumors were MGMT unmethylated and survived more than 2 years (longer than the expected median survival), there seemed to be a survival benefit from combined radiation and temozolomide compared to radiation alone.[22] In addition, because of issues with the reliability of the assay used to assess MGMT status in this EORTC-NCIC study, it has been debated whether these patients were incorrectly classified as MGMT unmethylated. Nevertheless, based on these data, a real albeit marginal benefit from temozolomide even in the unmethylated setting cannot be excluded. Therefore, it continues to be common practice to use the combination of temozolomide and radiation in all patients with newly diagnosed glioblastoma irrespective of MGMT methylation status.

1.2 Neratinib (PB-272, HKI-272)

Rationale & Proposed Biomarker Association

EGFR is a receptor tyrosine kinase that regulates cell growth and differentiation, and various mechanisms for oncogenic conversion in cancer have been described (Hynes and Lane, 2005). The evidence for a role of EGFR in oncogenesis is particularly compelling in glioblastoma where approximately 40% of tumors show amplification of the *EGFR* gene locus (Libermann et al, 1985) and about half of these *EGFR*-gene amplified cases express the constitutively active

mutant receptor *EGFRvIII* that harbors deletions of several exons within the extracellular ligand-binding domain (Yamazaki et al, 1988; Wong et al, 1992; Ekstrand et al, 1992).

Recent genome-wide cancer genomics studies have cataloged a diverse collection of *EGFR* gene abnormalities in glioblastoma (Brennan et al, 2013). These broad categories of *EGFR* mutations include:

1. Amplification of the *EGFR* genomic locus that may be non-mutated ('wild-type') or alternatively may be associated with one or more structural abnormalities in the *EGFR* gene (eg, deletions, point mutations) listed below,
2. *EGFRvIII*, the most common and most thoroughly-characterized *EGFR* structural gene variant in glioblastoma, characterized by deletion of 267 amino acids in the ECD and leading to a receptor which is unable to bind ligand yet is constitutively active (Gan et al, 2009),
3. Internal deletions of one or more exons in the *EGFR* gene, for example deletion of *EGFR* exons 12 &13, or exons 14 & 15, or exons 25, 26, and/or 27 (Brennan et al, 2013)
4. Missense (or 'point') mutations in the *EGFR* gene, for example but not limited to R108K, A289V, A289T, A289D, G598V mutations, in the extracellular domain of EGFR in 14% of glioblastomas (Figure 1). Cells transformed by expression of these EGFR mutants were sensitive to small molecule EGFR kinase inhibitors (Lee et al, 2006).
5. Novel fusion genes between the *EGFR* gene and one of a number of partner genes, for example *SEPT14* or *SEC61G* (Brennan et al, 2013).

Neratinib is an orally available small molecule inhibitor of EGFR, HER2, and HER4, that has been successful in clinical trials of HER2 positive breast cancer. Preclinical data demonstrates reduction of EGFR and HER2 autophosphorylation, downstream signalling, and growth in EGFR and HER2 dependent cell lines[22]. Neratinib inhibited the EGFR-overexpressing cell line (A431), but was much less active on MDA-MB-435 and SW620 (a breast and a colon cancer cell line, respectively) that are EGFR and HER2-negative (IB). Neratinib also inhibited the growth of EGFR-overexpressing A431 tumor xenografts, consistent with its effects on the cells in vitro, with maximum inhibition of tumor growth observed at the 40 mg/kg/day dose (76% inhibition on Day 15). The in vivo activity of neratinib was dependent on expression of HER2 or EGFR, as no significant antitumor effects were observed in xenografts of MCF-7 and MX-1 cells that express low levels of these receptors (IB). In a study (Study 3144A1-200-WW/B1891037) of NSCLC patients, while 51% of the patients showed stable disease as best response, the only partial responders were patients with EGFR mutations (IB).

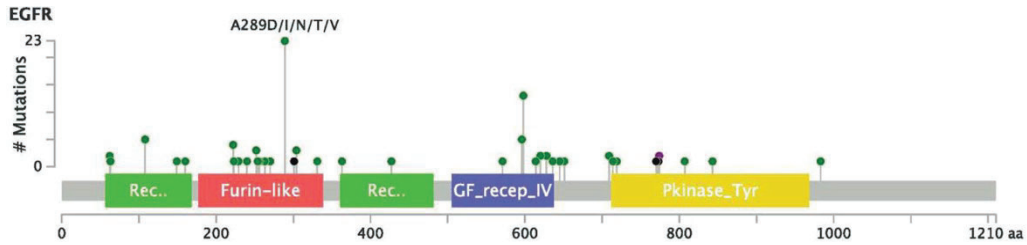


Figure 1. EGFR Mutations in Glioblastoma Multiforme

Source: cBioPortal for Cancer Genomics, accessed: 21OCT2013.

Preclinical data

Neratinib (PB-272) is a potent irreversible pan ERBB inhibitor. Neratinib is an orally available small molecule that inhibits EGFR, HER2, and HER4 at the intracellular tyrosine kinase domains. Neratinib reduces EGFR and ERBB2 autophosphorylation, downstream signaling, and the growth of EGFR- and HER2- dependent cell lines. Preclinical data show that neratinib has antitumor activity in EGFR- and/or HER2-expressing carcinoma cell lines, with cellular IC50 <100 nM (Rabindran et al, 2004) and has been shown to be selectively active against EGFRvIII in vivo using mouse models which mimic amplified EGFRvIII driven lung cancer when compared to erlotinib and other early generation EGFR inhibitors (Ji H, et al 2006 PNAS PMID: 16672372).

In glioblastoma, neratinib (HKI-272) has been shown to selectively cause cell death in cell lines harboring genetic activation of EGFR. In conventional GBM cell lines harboring extracellular domain mutations seen in GBM (Figure 2) and neratinib was much more effective than canertinib (CI-1033) and erlotinib (Vivanco et al., 2012).). Neratinib has been shown to exhibit potential for selective inhibition of amplified EGFRvIII in GBM patient derived cell line models (Figure 3, 4; Francis J et al 2014). While the Neratinib dose response range in GBM PDCLs is higher than in other cancer cell line studies, this is possibly due to the presence of ultra-high levels of EGF added to the defined media which sustains these primary cell cultures. Neratinib is significantly more potent than lapatinib in limiting growth of primary GBM cell lines (Figure 3,4). This is highly relevant motivation for studying neratinib in GBM given that negative human clinical trials with lapatinib have been attributed to the fact that tumor concentrations of the drug were estimated to be too low to induce cell death (Vivanco et al., 2012). The interactions of Neratinib with SNVs typicall seen in GBM has not yet been determined.

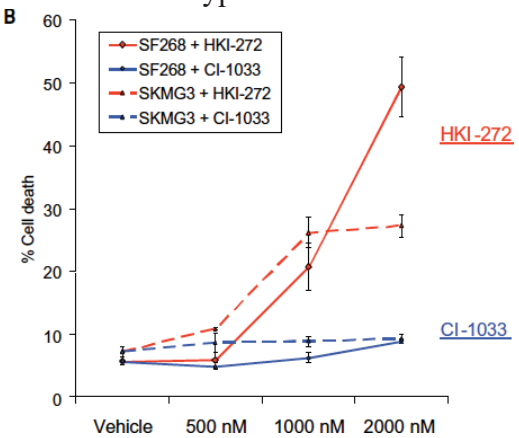


Figure 2: Cell death in GBM cell lines harboring extracellular domain mutations using neratinib (HKI-272) vs. another irreversible EGFRi (CI-1033)

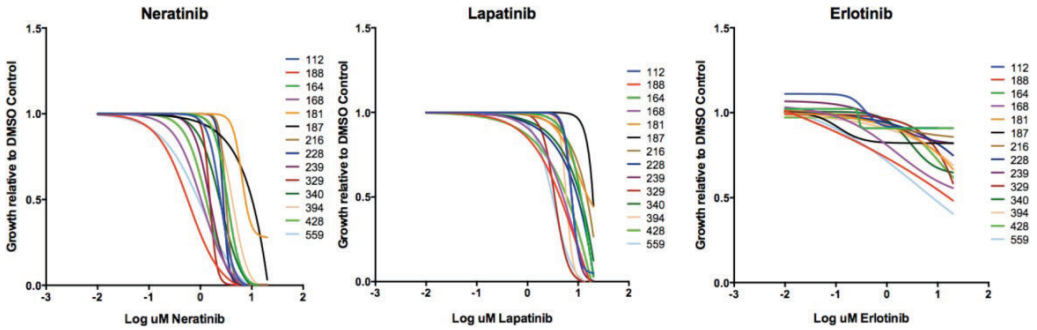


Figure 3: Growth inhibition of primary GBM tumor cell lines with neratinib (left), lapatinib (middle), or erlotinib (right).

Clinical data

Clinical benefit and antitumor activity have been shown in subjects with advanced or metastatic breast cancer who have received neratinib as a single agent or in combination with other anticancer agents. Positive results for neratinib 240 mg administered alone have been observed in women with HER2-positive locally advanced or metastatic breast cancer, with a response rate an overall response rate (ORR) of 53.8% and a PFS4 of 77.1% in patients without prior trastuzumab exposure (Investigator Brochure, IB). Clinical benefit has also been shown in 3 studies in which neratinib was co-administered with other anticancer therapies; ORR of 28.6% and PFS4 of 44.8% when combined with trastuzumab in women with HER2-positive advanced breast cancer in Study 202/B1891013; ORR of 72.7% when combined with paclitaxel in women with HER2-positive metastatic breast cancer in Study 203/B1891014; ORR of 41.4% when combined with vinorelbine in women with HER2-positive metastatic breast cancer without prior lapatinib exposure in Study 3144A1-2204-WW/ B1891015 (IB). Neratinib (240 mg qd) combined with capecitabine showed an ORR of 64% in patients with no prior lapatinib exposure in another study (Saura et al., 2014). Neratinib was also the second agent to "graduate" to phase III testing in the I-SPY 2 clinical trial based on improved pathologic response compared to standard therapy.

Importantly, treatment with neratinib has shown responses in progressive brain metastases (Freedman et al., 2014) and paclitaxel plus neratinib may decrease the incidence of CNS metastes by up to 50%. 479 patients with HER2+ MBC were randomized in an international phase II trial to receive either neratinib plus paclitaxel or trastuzumab plus paclitaxel (NEfERTT trial) [ClinicalTrials.gov identifier: NCT00915018]. The results were the subject of a press release on 13 November 2014, reporting similar PFS between the two treatment arms but less brain metastases in those treated with neratinib *versus* trastuzumab (7.4 *versus* 15.6%, $p =$ 0.006).Data are expected to be presented at a meeting in the near future.

Given the lack of rationale or data to combine with radiation therapy (RT) and the potentially real but small known benefit to adding TMZ to RT in patients with unmethylated tumors, our experimental plan for this arm is to combine RT with TMZ in the concurrent phase, but to replace TMZ with neratinib in the adjuvant phase.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria Specific to the Neratinib Arm

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration (section 4 of master protocol). Once the randomization assignment has been received following initial registration, all participants randomized to the neratinib arm must meet the following criteria prior to participating in the neratinib arm of the study.

2.1.1 Participants must be willing and able to provide written informed consent/assent for the neratinib arm of the INSIGhT trial.

2.1.2 Women of child bearing potential (women who are not free from menses for > 2 years, post hysterectomy/oopherectomy, or surgically sterile) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from date of intial dose and for 28 days following the last dose of neratinib. Men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) during intercourse with women of childbearing potential from date of initial dose and for 3 months following the last dose of Neratinib.

2.2 Second INSIGhT Registration: Registration to Neratinib Arm

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. Registration to the neratinib arm must occur following initial registration to master INSIGhT protocol and receipt of randomization assignment, and prior to the initiation of protocol therapy. Any participant not registered to their protocol specific assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria in section 2.1 of this sub-study appendix and a member of the study team will complete the protocol-specific eligibility checklist.

Following initial registration, any additional laboratory assessments prior to start of treatment will not be used to re-confirm eligibility. Refer to section 4 of this appendix for toxicity management between registration and start of study treatment.

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

2.2.1 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

2.2.2 Registration Process for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. The required forms for registration can be found in Appendix B.

Following registration, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Refer to Appendix B, Section 3.7 for registration details.

3. TREATMENT PLAN

Participants treated on the neratinib arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix with concomitant daily temozolomide (75 mg/m^2/day) as described in section 3.2, followed by a 28 (+14 days) day break, and followed by continuous once daily dosing of neratinib as described in section 3.4 below.

3.1 Definition of Standard Radiation Therapy

The patient must undergo MRI based treatment planning (CT with contrast-based planning only if patient unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). The margin may be reduced around natural barriers to tumor growth, and also to allow sparing of organs at risk, if necessary. The volume must be treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast-enhancing region is acceptable. Treatment or no treatment of the T2/FLAIR abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 52 calendar days. Maximum dose (defined as a volume greater than 0.03 cc) to critical structures include: 60 Gy to the brainstem, 56 Gy to the optic chiasm, 55 Gy to the optic nerves, and 50 Gy to the retinae.

Participants are permitted to have radiotherapy as described in this section performed at any NCI funded cooperative group site. Prospective Overall PI approval, or approval by his designee (other Coordinating Center radiation oncologists), is required for any radiotherapy site that is not an NCI funded cooperative group site. At the discretion of the DFCI Coordinating Center, a radiation plan may be requested to be prospectively approved for a non-NCI site prior to initiating radiotherapy at the site. Any questions regarding permitted radiotherapy sites should be directed to the DFCI Coordinating Center or Overall PI Patrick Y. Wen, MD.

3.2 Concomitant Temozolomide during Radiation Therapy

Treatment on concomitant therapy should begin no later than 6 weeks from surgery.

Temozolomide 75 mg/m^2/day will be administered orally on a continuous daily dosing schedule for a maximum of 49 days. Temozolomide will be initiated on Day 1 of radiation therapy, and the last dose will ideally be the last day of radiation; however, temozolomide may be administered for 42 days, or per your site's institutional policy / standard.

The drug will be administered orally approximately 2-3 hours before each session of radiotherapy. During weekends or weekdays without radiotherapy (Saturday and Sunday), the drug should be taken in the morning when possible. The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The daily dose will be rounded to the nearest 5 mg.

No dose reductions are allowed during the concomitant phase of treatment. If a participant experiences a toxicity related to temozolomide during the concomitant phase of treatment, then temozolomide dosing will be interrupted according the rules described in Table 4.2 of this appendix.

Temozolomide will be administered on an outpatient basis. The investigator will instruct the participant to take the drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Participants will be instructed to fast at least 1 hour before and 1 hour after temozolomide administration. Prophylaxis with a 5-HT3 antagonist is recommended prior to administration of temozolomide doses and should be administered orally approximately 30 to 60 minutes before temozolomide treatment. Temozolomide should be taken with a glass of water and consumed over as short a time as possible. Participants should swallow the capsules as a whole and not chew them. Additional drug administration instructions, including missed dose policy, are described in section 6.1.8 of this appendix and are included in the participant pill diary (section 11 of this appendix).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires a temozolomide dose delay of > 28 days from the previous dose, the participant must be discontinued from further temozolomide treatment. If a participant discontinues temozolomide treatment due to toxicity, the participant may continue study treatment with adjuvant cycles of neratinib as described in section 3.4 below. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen, MD at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Participants will keep a temozolomide diary (see section 11 of this appendix). After completion of radiation, the diary will be returned.

3.3 Rest Phase

During the 28 day (+14 days) break after completion of radiotherapy, temozolomide will not be administered.

3.4 Adjuvant (Post-Radiation) Neratinib Treatment

Adjuvant cycles of neratinib should begin no sooner than 28 days (+ 14 days) following the completion of radiation therapy. Participants cannot begin adjuvant neratinib if they meet any criteria requiring a dose modification as outlined in section 4.3 of this appendix. All adjuvant cycle 1, day 1 assessments (as noted in section 7 study calendar of this appendix) must be resulted and reviewed prior to initiating treatment with neratinib.

The study drug, neratinib, will be administered on an outpatient basis. The investigator will instruct the participant to take the study drug exactly as specified in the protocol. No investigational or commercial agents or therapies other than those described in this appendix may be administered with the intent to treat the patient's malignancy.

Participants should be instructed to take the dose of neratinib by mouth with food, preferably in the morning daily, starting at 240mg per day. **Cycle length will be 28 days, even if treatment is held mid-cycle for toxicity. Primary prophylactic use of antidiarrheal medication will be required for all enrolled subjects (see below section 3.5.15 for more details)**. Participants should swallow tablets as a whole and not chew them. Participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A4 interaction. Additional drug administration instructions, including missed dose policy, are described in section 6.2.8 of this appendix and are included in the neratinib pill diary (see section 12 of this appendix).

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires a neratinib dose delay of > 28 days from the previous dose, the participant must be discontinued from treatment completely. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen, MD at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

Participants will keep a medication diary (see section 12 of this appendix). At the end of each cycle, the diary will be returned and a new one will be given to the participant. Participants are to return all pill bottles and unused pills.

3.5 General Concomitant Medication and Supportive Care Guidelines

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

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

3.5.1 Strong CYP3A inhibitors and CYP3A inducers are **prohibited**. In vitro studies suggest that neratinib is a sensitive CYP3A4 substrate. Co-administration of neratinib with strong CYP3A4 inhibitors is predicted to increase the systemic exposure to neratinib; likewise CYP3A inducers can be expected to decrease systemic exposure to neratinib, possibly resulting in sub-therapeutic drug levels. Refer to Appendix C of master INSIGhT protocol for a list of prohibited drugs. Please note that this list may not be comprehensive.

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

3.5.3 The solubility of neratinib is pH dependent and treatments that alter gastrointestinal pH such as proton pump inhibitors (PPIs), H2-receptor antagonists, and antacids may lower the solubility of neratinib. It has been observed that a single 240-mg dose of neratinib combined with lansoprazole may decrease neratinib AUC by up to 70%. It is unknown whether separating PPI and neratinib doses reduce the interaction.

3.5.3.1 PPIs should be avoided whenever possible.

3.5.3.1.1. Recommend that Teams contact the DFCI NOC Coordinating Center when there is no alternative and/or treating team wants to use PPIs, so that they may run by Overall PI for feedback.

3.5.3.2 If an H2-receptor antagonist such as ranitidine is required, neratinib should be taken 10 hours after the H2-receptor antagonist dosing and at least 2 hours before the next dose of the H2-receptor antagonist.

3.5.3.3 If antacids are necessary, the antacid dose and the neratinib dose should be separated by 2 to 4 hours.

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

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

3.5.6 Anti-seizure medications should be used as indicated. Only participants receiving non-EIAEDs are eligible (although protocol does allow for patients to register and initiate treatment with Temodar and radiation therapy while tapering off EIAEDs). If for unavoidable clinical reasons (emergency department visit, severe allergies, toxicities, etc.) a participant’s AED is switched to another AED, the following guidelines must be followed if applicable:

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

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

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

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

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

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

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

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

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

3.5.15 **Concurrent Prophylactic Administration of Loperamide**

Investigators must ensure that subjects have loperamide on hand when starting to take the investigational product. Loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is used, the reason must be documented in the source documents. Acceptable reasons are non-tolerance of loperamide or lack of efficacy. A prescription for loperamide will be provided for the subject with the instruction to have loperamide on hand prior to taking the first dose of investigational product. The subject can also obtain loperamide "over-the-counter" prior to taking the first dose of investigational product on Day 1.

- Inform patients that they will experience diarrhea while taking neratinib
- Administer loperamide: For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be administered orally withthe first dose of neratinib.
- After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be administered orally twice a day (total 8 mg a day) through the first cycle of therapy (Day 28) from start of neratinib dosing.
- Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day).

Loperamide Dosing

Day	Loperamide Dose
1-14	Daily dose of 12 mg in 3 divided doses of 4 mg
15-28	Daily dose of 8 mg in 2 divided doses of 4 mg
>28	Daily dose as needed (not to exceed 16 mg per day)

Loperamide Dose Adjustment

Patients are expected to take loperamide prophylaxis as directed. However, patients may require individualization of loperamide prophylaxis dose (up to a maximum dose of 16 mg per day) with the goal of titrating to 1-2 bowel movements a day.

- For patients who develop diarrhea during Cycle 1, loperamide should be increased up to a maximum of 16 mg a day.
- If a patient is unable to tolerate loperamide due to symptomatic constipation, loperamide should be held until after the first bowel movement and then resumed at a dose reduced by one level.
- For recurrent symptomatic constipation events, hold loperamide until after the first bowel movement and then resume at a dose reduced to the next lower dose level.
- If a patient is unable to tolerate once-daily loperamide due to constipation, hold loperamide and discuss subsequent loperamide dosing with the Overall PI.
- Neratinib dosing should continue if loperamide is held.

Recommended dose reductions for loperamide are listed in the table below.

Loperamide Dose Reduction Levels for Constipation

Dose Level	Loperamide Dose	Tablets/Capsules per day
0	4 mg TID	6 tablets/capsules a day
-1	4 mg BID	4 tablets/capsules a day
-2	2 mg TID	3 tablets/capsules a day
-3	2 mg BID	2 tablets/capsules a day
-4	2 mg once a day	1 tablet/capsule a day

Abbreviations: BID = twice daily; mg=milligrams; TID= three times daily.

Refer to section 4.3.2 of this appendix for additional guidelines on management of diarrhea.

3.6 Criteria for Taking a Participant Off Protocol Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

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

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Patrick Y. Wen, MD, at 617-632-2166 or pwen@partners.org.

3.7 Duration of Follow Up

Participants will be followed until death with monthly visits, telephone contact, or medical record review. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Refer to section 7 study calendar within this appendix for follow-up requirements and time points.

3.8 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

4. DOSING DELAYS/DOSE MODIFICATIONS

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

4.1 Anticipated Toxicities

In order for an event to be considered expected (known correlation to study drug/treatment) for the purposes of adverse event reporting, the event must be:

- Included in this section for Neratinib.
- Included in this section or included in the package insert or the informed consent document as a potential risk for Temozolomide and radiation therapy.

NOTE: For events that are secondary to an event deemed expected with a study agent/modality (e.g. rectal pain or hypokalemia as a result of diarrhea or gait disturbance as a result of edema cerebral), please record as "possibly related to" and "expected with" the agent/modality.

4.1.1 Anticipated Toxicities for Radiation Therapy

A list of adverse events of all grades suspected to be radiation therapy treatment related, organized by CTCAE v4.03 category, includes:

- EAR AND LABYRINTH DISORDERS – external ear inflammation; other: dryness of ear canal; other: hardening of ear canal wax; external ear pain; other: hearing loss
- ENDOCRINE DISORDERS - other: hypophysitis, or hypopituitarism
- EYE DISORDERS – cataract; other: decreased vision
- GASTROINTESTINAL DISORDERS – nausea; vomiting
- GENERAL DISORDERS – fatigue
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – dermatitis radiation; injury other: optic nerve
- INVESTIGATIONS –lymphocyte count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED – treatment related secondary malignancy

- NERVOUS SYSTEM DISORDERS – headache; seizure; memory impairment; cognitive disturbance; somnolence; dysgeusia; central nervous system necrosis; edema cerebral; other: tumor inflammation**
- PSYCHIATRIC DISORDERS – personality change
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – scalp pain; other: scalp redness; alopecia

4.1.2 Anticipated Toxicities for Temozolomide

A list of adverse events of all grades suspected to be temozolomide treatment related, organized by CTCAE v4.03 category, includes:

- BLOOD AND LYMPHATIC SYSTEM DISORDERS – anemia; febrile neutropenia; bone marrow hypocellular
- GASTROINTESTINAL DISORDERS – constipation; nausea; vomiting; diarrhea
- GENERAL DISORDERS – gait disturbance; fatigue
- IMMUNE SYSTEM DISORDERS – allergic reaction
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – bruising; hemorrhage
- INVESTIGATIONS – neutrophil count decreased; lymphocyte count decreased; white blood cell decreased; platelet count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness*
- NERVOUS SYSTEM DISORDERS – dizziness; memory impairment; headache; seizure
- PSYCHIATRIC DISORDERS – insomnia
- REPRODUCTIVE SYSTEM AND BREAST DISORDERS – infertility
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – alopecia

4.1.3 Anticipated Toxicities for Neratinib

A list of adverse events of all grades suspected to be neratinib treatment related according to review of Investigator's Brochure, organized by CTCAE v4.03 category, includes:

- GASTROINTESTINAL DISORDERS: abdominal distention, dry mouth
- INVESTIGATIONS: weight loss; aspartate aminotransferase increased; alanine aminotransferase increased; blood bilirubin increased
- INFECTIONS AND INFESTATIONS – Urinary tract infection
- MUSCUSKELETAL AND CONNECTIVE TISSURE DISORDERS – Muscle spasms
- RESPIRATORY, THORACICAND MEDIASTINAL DISORDERS – Epistaxis; renal failure, blood creatinine increased
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – erythema multiforme; rash pustular; rash follicular; rash generalized; dry skin; skin fissure; nail discoloration; paronychia; onychoclasis

* "Generalized muscle weakness" to also include other CTCAE terms inclusive of a muscle weakness

** As CTCAE v. 4 recognizes 'Edema cerebral' only as a Gr4 event, please record events of 'Edema cerebral' deemed by Investigator to be Gr1-Gr3 or Gr5 as 'Nervous system disorders, Other: Tumor inflammation' (Gr1-Gr3 or Gr5, accordingly).

4.2 Dose Modifications/Delays for Temozolomide

4.2.1 No temozolomide dose reductions are allowed during the concomitant phase of treatment. If a participant experiences a toxicity related to temozolomide during the concomitant phase of treatment, then temozolomide dosing will be interrupted according the rules described in Table 4.2 of this appendix.

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

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

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

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

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

4.2.4.1 NOTE: Study treatment may be held > 28 days in order to allow for surgical pathology to determine progression versus pseudoprogression outside of the 12-week consideration mark if it is prospectively confirmed with Overall PI to be clinically appropriate to do so.

4.2.5 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 4.2 of this appendix, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of study treatment. All SAEs must be reported as detailed in Section 5.3 of this appendix.

Table 4.2: Criteria for dose-modification and re-initiation of temozolomide treatment

For toxicities attributable to temozolomide (considered at least possibly related), Table 4.2 should be adhered to as noted below. When the treating investigator feels that a hold of temozolomide is warranted for patient safety even though the toxicity is unlikely or unrelated to temozolomide, discussion with the Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Toxicity (organized per CTCAE v 4.03)	Concomitant Temozolomide
Neutropenia - Grade 2 (ANC 1.0 - 1.4 x 109/L)	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.
Neutropenia - Grade 3 (ANC 0.5 - 0.9 x 109/L)	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.
Neutropenia - Grade 4 (ANC < 0.5 x 10^9/L)	Discontinue TEMOZOLOMIDE
Thrombocytopenia - Platelet count: 50 - 99 x 10^9/L	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, then resume TEMOZOLOMIDE at the current dose level.
Thrombocytopenia - Platelet count: 10 - 49 x 10^9/L	Interrupt until platelet count recovers to ≥ 100 x 10^9/L, then resume TEMOZOLOMIDE at the current dose level.
Thrombocytopenia - Platelet count: < 10 x 10^9/L	Discontinue TEMOZOLOMIDE
Non-hematologic toxicity (except for alopecia, nausea, vomiting, constipation, weight loss, & anorexia) - Grade 2	Interrupt until resolved to ≤ grade 1, then resume TEMOZOLOMIDE at the current dose level.
Non-hematologic toxicity (except for alopecia, nausea, vomiting, constipation) - Grade 3	Discontinue TEMOZOLOMIDE
Non-hematologic toxicity (except for alopecia, nausea, vomiting, constipation) - Grade 4	Discontinue TEMOZOLOMIDE

4.3 Dose Modifications/Delays for Neratinib

All participants will be initially treated at Dose Level 0.

Neratinib Dose Levels

Dose Level	Dose of Neratinib
0 (starting dose)	240 mg daily
-1	160 mg daily
-2	120 mg daily

4.3.1 General Dose Adjustments for Neratinib-Related Toxicities

Subjects should be withdrawn from the study if the 120-mg dose level of neratinib is not tolerable, or if the subject fails to recover to NCI grade 0 to 1 (or to within baseline of starting values for preexisting laboratory abnormalities) from treatment-related toxicity, leading to treatment delay of >4 weeks. Missed dose(s) of the investigational product will not be made up.

Table 4.3.1 should be adhered to for all toxicities attributable (considered at least possibly related) to neratinib as noted below unless otherwise specified in this appendix. If a participant experiences a toxicity unlikely or unrelated to treatment with neratinib but may still warrant a hold or reduction of study drug for safety, discussion and written approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Table 4.3.1: General criteria for dose-modification and re-initiation of neratinib treatment

NCI CTCAE v.4.03	Action
Grade 2 Neutropenia/Thrombocytopenia and non-hematologic toxicities	
• 1st appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at the starting dose level.
• 2nd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.
• 3rd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.
• 4th appearance	• Discontinue **neratinib** permanently.
Grade 3 adverse reaction	
• 1st appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 160 mg.
• 2nd appearance	• Hold **neratinib** until event resolves to Grade ≤1; then resume **neratinib** at 120 mg.
• 3rd appearance	• Discontinue **neratinib** permanently.
Grade 4 adverse reaction	
• 1st appearance	• Discontinue **neratinib** permanently OR if Investigator deems it to be in the patient's best interest to continue, hold **neratinib** until resolved to Grade ≤1; then resume **neratinib** at 160 mg. • If the event occurs again despite one dose reduction, permanently discontinued **neratinib.**

4.3.2 Guidelines for the Management of Diarrhea

Diarrhea is the major DLT of neratinib with onset typically occurring early in the course of treatment (during the first few weeks of treatment). Primary prophylactic use of antidiarrheal medication is **mandatory** for all enrolled subjects receiving neratinib at any

dose for cycle 1. Loperamide is the recommended standard therapy to treat diarrhea in this study. If alternative antidiarrheal medication is proposed, this should be discussed with the Principal Investigator and the reason documented in the source documents. Second-line antidiarrheal treatments and adjunctive therapies (i.e., octreotide [SANDOSTATIN®]) are also recommended for use when appropriate at the treating investigator's discretion.

The investigator or designee must review with the subject the Patient Instructions for the Management of Diarrhea (section 14 of this appendix) and the Antidiarrheal Dosing Diary (section 13 of this appendix) for the subject's daily recording of investigational product dose and use of loperamide use and/or other antidiarrheals during cycle 1.

Participants should be strongly encouraged to contact their treating team/physician as soon as possible following the first signs of diarrhea. Both the subject and the investigator or designee must sign the supplemental document Patient Instructions for the Management of Diarrhea (section 14 of this appendix) for the management of diarrhea. Copies of both documents are handed to the subject before leaving the site with investigational product on Day 1 with clear instructions to contact the investigator or designee in the event of de novo onset or persistent ≥ grade 2 diarrhea to discuss the appropriate course of treatment. In addition, the Investigator or designee will contact the subject at 1 day, 2 days, and 3 days after the first dose of study drug is administered to inquire about any diarrhea.

A script for loperamide (or other antidiarrheal) must be provided prior to participant receiving day 1 with neratinib. It is very important to initiate treatment with loperamide concomitantly with the first dose of neratinib to minimize occurrence and severity of diarrhea.

Mandatory Prophylactic Cycle 1 Dosing Instructions

- Administer loperamide:
  - Cycle 1, Day 1: initial dose of 4 mg (2 tablets/capsules) with the first dose of neratinib, followed by 4mg TID for a total of loperamide 16 mg within 24 hours of cycle 1, day 1 neratinib dose.
  - Cycle 1, Days 2-14: loperamide 4mg TID for a total of 12mg/day
  - Cycle 1, Days 15-28: loperamide 4 mg BID for a total of 8 mg/day whether the patient is experiencing diarrhea or not.
  - Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day).
- For patients with persistent Grade 1 diarrhea (<4 stools per day above baseline) on loperamide, Lomotil® (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 to 8 hours may be added (or equivalent).
- For Grade 2 diarrhea during the first 28 days (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 µg subcutaneous [SC] injection 3 times a day, or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg by intramuscular (IM) injection (or equivalent).

After resolution of diarrhea, loperamide prophylaxis can be increased in 2 mg

increments with the goal of titrating to 1-2 bowel movements a day.

- The Investigator or suitably trained and qualified delegate (e.g., MD, RN, NP, etc.) must contact the patient by phone on Cycle 1 Day 2, Cycle 1 Day 3, and Cycle 1 Day 4 after the first dose of neratinib to inquire about compliance with loperamide and diarrhea or any other adverse events. (These phone calls are very important and should be recorded in the clinical records together with response from the patient and action taken.)
- Instruct patients to promptly report diarrhea symptoms.
- Instruct patient to report the number of stools per day and the dose of any anti-diarrheal medication taken each day for the first 28 days of therapy.

For new onset uncomplicated grade 1 or grade 2 diarrhea (in Cycle 2 and beyond)

- **Recommended dietetic measures**
  - Stop all lactose-containing products
  - Drink 8 to 10 large glasses of clear liquids per day
  - Eat frequent small meals
  - Recommend low fat regimen enriched with bananas, rice, applesauce and toast (BRAT diet) until resolution of diarrhea.
- **Recommended pharmacological treatment**
  - Administer loperamide: initial dose of 4 mg (2 tablets) with the first bout of diarrhea followed by 2 mg (1 tablet) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (< 4 stools/day).
  - For patients with persistent grade 1 diarrhea on a maximum dose of loperamide (16 mg per day), Lomotil (diphenoxylate hydrochloride and atropine sulfate) 1 tablet (2.5 mg) every 6 hours to 8 hours may be added.
  - For grade 2 diarrhea (4 to 6 stools per day above baseline, despite intensive anti-diarrheal therapy), consider adding octreotide (short-acting) 150 micrograms SC TID; or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg IM.

For grade 3 or grade 4 diarrhea with complicating features (dehydration, fever, and/or grade 3-4 neutropenia

- **Recommended dietetic measures (same as above)**
- **Recommended pharmacologic treatment**
  - Administer loperamide: initial dose of 4 mg (2 tablets) with the first bout of diarrhea followed by 2 mg (1 tablet) every 4 hours or after every unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (< 4 stools/day).
  - Administer octreotide (SANDOSTAINE®) [100-150 µg SC BID or IV (25-50 µg/h) if dehydration is severe, with dose escalation up to 500 µg SC TID]
  - Use intravenous fluids as appropriate
  - Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3-4 neutropenia.

Stool cultures should be done to exclude infectious causes of grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or grade 3 or 4 neutropenia) per the investigator's discretion. Results from occult blood, fecal leukocyte stain, Clostridium difficile, Campylobacter, Salmonella, and Shigella testing, when performed, should be reported.

Subjects with significant diarrhea who are unresponsive to medical treatment may require treatment interruption or dose reduction as listed in table below.

Table 4.3.2 Gastrointestinal Toxicities Requiring Dose Adjustment of Neratinib

Toxicity (organized per CTCAE v 4.03)	Actions
Grade 1 Diarrhea [Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.] **OR** **Grade 2 Diarrhea** [Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline;] lasting <5 days **OR** **Grade 3 Diarrhea** [Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline limiting self-care activities of daily living (ADL)] **lasting < 2 days**	• Adjust anti-diarrheal treatment as per guidelines for management of diarrhea in section 4.3.2 of this appendix. • Continue **neratinib** at full dose. • Instruct patient to follow dietetic recommendations in the guidelines for management of diarrhea. • Fluid intake of ~2L should be maintained to avoid dehydration. • Once the event resolved to ≤ grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.

Persisting and intolerable **Grade 2 Diarrhea** lasting >5 days despite being treated with optimal medical therapy, or associated with fever, dehydration, **or grade 3-4 neutropenia** **OR** **Grade 3 Diarrhea** lasting > 2 days despite being treated with optimal medical therapy, or associated with fever, dehydration, **or grade 3-4 neutropenia** **OR** **Any Grade 4 diarrhea** [Life-threatening consequences; urgent intervention indicated]	• Adjust anti-diarrheal treatment as per guidelines for management of diarrhea in section 4.3.2 of this appendix. • Hold **neratinib** until recovery to ≤ grade 1 or baseline. • Instruct patient to follow dietetic recommendations of the guidelines for management of diarrhea. • Fluid intake of ~2L should be maintained, intravenously if needed. • If recovery occurs: o ≤1 week after withholding treatment, resume same dose of **neratinib**. o Within 1-3 weeks after withholding treatment, reduce **neratinib** dose to the next lower dose level. o If event recurs and the **neratinib** dose has not already been decreased, reduce **neratinib** dose to the next lower dose level. o If subsequent events occur, reduce **neratinib** dose to the next lower dose level. • Once the event resolved to ≤ grade 1 or baseline, start loperamide 4 mg with each subsequent **neratinib** administration.
	• If event recurs and the **neratinib** dose has already been reduced at the lowest level, discontinue **neratinib**.

4.3.3 Guidelines for the Management of Changes in Liver Function Tests

Changes in LFTs have been reported in subjects taking neratinib. Subjects experiencing grade 3 or 4 diarrhea requiring IV hydration and associated with any signs or symptoms of hepatotoxicity such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia should be evaluated for LFT changes.

Table below should be adhered to for AEs determined to be at least possibly related to neratinib.

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria in the table below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The possibility of hepatic neoplasia (primary or secondary) should also be considered. During evaluation of potential hepatotoxicity, bilirubin should be fractionated and

prothrombin time should be measured. Also, liver imaging should be obtained for subjects with any signs or symptoms of hepatotoxicity and/or grade 3 or greater LFT elevations, or as clinically indicated.

Table 4.3.3 Liver Function Test Toxicities Requiring Dose Adjustment of Neratinib

Event (Based on NCI CTC4.0)	Action
Grade 3 ALT (>5-20x ULN) **OR** Grade 3 Bili (>3-10x ULN) and direct bili ≥ 35% of total bili	• For participants with AST/ALT <grade 1 at baseline, resume neratinib at one dose level lower if recovery to baseline occurs within 21 days. • If grade 3 AST, ALT or bilirubin recurs despite one dose reduction, resume neratinib at a further dose reduction if recovery to baseline occurs within 21 days. • If grade 3 AST/ALT or bilirubin occurs despite this second dose reduction, permanently discontinue neratinib. Report as SAE. • Evaluate alternative causes.
Grade 4 AST/ALT (>20x ULN) **OR** Grade 4 Bilirubin (>10x ULN)	• Permanently discontinue investigational product (IP) • Evaluate alternative causes.

ALT > 3x ULN **and** Total bilirubin > 2x ULN **and** Alkphos < 2x ULN. (Potential Hy's law indicators of drug-induced liver damage).	Hold IP and immediately contact the PI to discuss next steps, including evaluation of alternative causes, and management of IP. The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. Laboratory assessment must include: repeat AST and ALT, albumin, total bilirubin, direct bilirubin, PT, PTT and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, concomitant medications, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the criteria mentioned (i.e., ALT > 3 x ULN associated with bilirubin >2 x ULN and alkaline phosphatase <2 x ULN), with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases, irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. •Contact Puma immediately to discuss next steps, including evaluation of alternative causes, and management of investigational product(s). • Report as SAE.
Signs or symptoms related to liver injury (abdominal pain, fever, jaundice, rash, eosinophilia, or drop in performance status) with either: Grade 2 ALT (>3-5x ULN), **or** Grade 2 ALT (>3-5x ULN) **and** Grade 2 Bili (>1.5-3x ULN) and direct bili ≥ 35% of total bili.	• Permanently discontinue IP. • Evaluate alternative causes.

4.3.4 Guidelines for the Management of Pulmonary Toxicity

Guidelines for adjusting doses of neratinib in the event of pulmonary toxicities are shown in Table 4.3.4. Interstitial lung disease, which can sometimes be fatal, has been reported with other oral tyrosine kinase inhibitors that target EGFR ±HER2 (*ERBB2*), including lapatinib, gefitinib, and erlotinib. Rare cases of pneumonitis (0.6%) and lung infiltration (0.4%) have been reported in patients treated with neratinib monotherapy, and considered drug-related. Patients receiving neratinib should be monitored for acute onset or worsening of pulmonary symptoms such as dyspnea, cough, and fever and treated appropriately.

Table 4.3.4: Pulmonary Toxicities Requiring Dose Adjustment of Neratinib

NCI CTCAE V4.03	Action
Grade 2 Pneumonitis/Interstitial Lung Disease [Symptomatic; medical intervention indicated; limiting instrumental ADL]	• Hold **neratinib** until recovery to ≤ Grade 1 or baseline. • Reduce **neratinib** to 160 mg or discontinue **neratinib** as per Investigator's best medical judgment.
Grade ≥3 Pneumonitis/Interstitial Lung Disease [Severe symptoms; limiting self-care ADL; oxygen indicated]	• Discontinue **neratinib** permanently.

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (section 4.1 of this appendix) and the characteristics of an observed AE (Section 5.2 of this appendix) will determine whether the event requires expedited reporting **in addition** to routine reporting.

This section specifies reporting requirements to the FDA, Overall PI/Coordinating Center, DF/HCC IRB, and manufacturer as applicable.

5.1 Expected Toxicities

Refer to section 4.1 of this appendix for expected toxicities for assigned study treatment arm.

5.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in section 4.1 of this appendix should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

- **Serious Adverse Event (SAE) Definition**:
  A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:
    - Results in death
    - Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
    - Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
    - Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
    - Is a congenital anomaly/birth defect;
    - Constitutes an important medical event. Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

5.3 Expedited Adverse Event Reporting

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

5.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event that is *Serious, Unexpected,* and there is a *Reasonable Possibility* (i.e., possible, probable, or definitive attribution) the Adverse Event is related to the study intervention.

5.3.3 Expedited Reporting Guidelines to Overall PI/Coordinating Center

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

External investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the AE form should be forwarded to the Overall PI within the timeframes detailed in the table below. The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

In addition to local IRB reporting policies, all sites are required to following the Table 5.3.3 expedited reportable AE requirements:

NOTE: Until patients initiate treatment with Neratinib on study, please report per Table 5.3.3 'Expedited AE Reporting by external sites to Coordinating Center/Overall PI' of Appendix E (Control Arm).

Table 5.3.3 Expedited AE Reporting Requirements

Adverse Event Characteristics				Reporting Requirement
Seriousness	**Toxicity**	**Known Correlation[f]**	**Attribution to Neratinib**	**Overall PI (Patrick Y. Wen, MD) at the DFCI Coordinating Center Via Email [b] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**
Serious[e]	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [a]
Non-Serious	Grade 4	Any (Expected or Unexpected)	Any	Within 5 working days from notification [a]
Non-Serious	Grade 2 or 3	Unexpected	Possible, probable, definite	Within 7 working days from notification [a]

a. In the event that the participating investigator/site team does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator/site team is to report the event within the required hours/days noted above after learning of it and document the time of his or her first awareness of the adverse event. The initial report must be as complete as possible, including assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE or reportable AE is required.
b. Email the Medwatch 3500A form, reportable AE coversheet (section 10 of this appendix), and the local IRB SAE report (if applicable) to the DFCI Coordinating Center with the subject title as "INSIGHT SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Patrick Y. Wen, and to the DFCI Coordinating Center personnel.
c. Reportable AE Coversheet is found in section 10 of this appendix. The coversheet contains all FAX numbers/e-mails and needed for reporting purposes.
d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm
e. Seriousness is defined in section 5.2 of this appendix.
f. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Anticipated Toxicities list (protocol section 4.1 of this appendix) which is derived from the Investigator's Brochure and/or package insert (if applicable).

5.3.4 How to report AEs to PUMA & DFCI Coordinating Center/Overall PI

1. Document/describe reportable AE(s) on the following:
    a. MedWatch 3500A
        i. downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. DFCI Reportable AE Coversheet – INSIGhT Neratinib Arm
        i. Coversheet can be found in section 10 of this appendix. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.
2. Scan and email above documents to NeuroOnc_SAE@dfci.harvard.edu with the subject title "INSIGHT SAE"
    a. All AE reports received at this account are forwarded immediately to Overall Principal Investigator (Dr. Patrick Y. Wen), and to Coordinating Center personnel.
    b. If available and applicable, also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.

5.3.5 Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

- Lymphopenia (grades 2-4)
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for treatment of patient's underlying disease after coming off study treatment (e.g. admission after patient is removed from active study treatment for craniotomy)

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

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

5.5 Expedited Reporting to Hospital Risk Management

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

5.6 Routine Adverse Event Reporting

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

5.7 Reporting to Puma Biotechnology, Inc.

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events, in addition to being reported to the FDA by the investigator, must be reported by email to **Puma Biotechnology, Inc.** as follows:

For expedited reports, DFCI Coordinating Center will send the MEDWATCH report to the Company no later than seven (7) days for initial life-threatening and death reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reaction (SUSAR) as assessed by the investigator for causality and by the Investigator-Sponsor for causality and expectedness based on section 4.1 of this appendix from the time of receipt of the SAE by DFCI Coordinating Center. For non-expedited reports (i.e., unrelated to study drugs or listed/expected event), DFCI Coordinating Center will send the MEDWATCH report to the Company no later than thirty (30) days from the time of receipt of the SAE by DFCI OHRS.

By e-mail to PumaSAE@parexel.com

SAEs brought to the attention of the investigator at any time after cessation of neratinib and considered by the investigator to be related or possibly related to neratinib must be reported to **Puma Biotechnology, Inc.** if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged from the study.

6. PHARMACEUTICAL INFORMATION

6.1 Temozolomide

6.1.1 Description

The chemical name of Temozolomide is 3,4-dihydro-3methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide and the molecular weight is 194.15, which acts as an alkylating agent.

In humans, the terminal elimination half-life ($t_{1/2}$) in plasma ranges from approximately 1.6 to 1.88 hours. Following oral administration, the drug, Temozolomide, is rapidly absorbed and then hydrolyzed to the active metabolite 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC spontaneously degrades to CO_2 and 5-aminoimidazole-4-carboxamide (AIC) and excreted via the urine. CYP isoenzymes play an only minor role in Temozolomide metabolism.

6.1.2 Form

Temozolomide drug will be supplied commercially and should be ordered per local policy. The drug products are stable when stored according to instructions on the label.

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of Temozolomide and the inactive ingredients sodium starch glycolate, tartaric acid, stearic acid, and colloidal silicon dioxide.

The body of the capsules is made of gelatin, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength.

6.1.3 Storage and Stability

Temozolomide is stable at room temperature.

6.1.4 Compatibility

There are no known compatibility issues.

6.1.5 Handling

Routine chemotherapy handling is recommended.

6.1.6 Availability

Temozolomide is available through special pharmacy and can be prescribed by the treating physician.

6.1.7 Preparation

None

6.1.8 Administration

- Temozolomide capsules should not be opened or chewed; they must be swallowed whole with a glass of water one hour before or after food and other medications.
- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.
- If the participant forgets to take his/her temozolomide dose more than 10 hours from the last dose, then that dose should be withheld and temozolomide should be restarted at the time of the next planned dose.

6.1.9 Ordering

Temozolomide drug will be supplied commercially and should be ordered per local policy.

6.2 Neratinib

6.2.1 Description

Neratinib (PB-272) is a potent irreversible pan erbB inhibitor. Neratinib is an orally available small molecule that inhibits erbB-1, erbB-2, and erbB-4 at the intracellular tyrosine kinase domains, a mechanism of action that is different from trastuzumab.

Preliminary pharmacokinetic analyses demonstrated that neratinib absorption was relatively slow, and the maximum concentration (Cmax) was generally attained within 3 to 6 hours. After oral administration, the neratinib Cmax and area under the concentration versus time curve (AUC) increased in a dose-dependent manner in general. Mean steadystate Cmax and AUC values were 70.1 ng/mL and 975 ng·h/mL for the 180-mg dose group, respectively, 73.5 ng/mL and 939 ng·h/mL for the 240-mg dose group, respectively, 90.4 ng/mL and 1333 ng·h/mL for the 320-mg dose group, respectively, and 105 ng/mL and 1704 ng·h/mL for the highest dose of 400 mg, respectively. The neratinib exposure (AUC) increased 1.2- to 2.7-fold (mean accumulation ratio) when comparing the steady-state exposure on day 21 after repeated daily administration with the exposure on day 1 after administration of 80 to 400 mg of neratinib. The mean accumulation ratio was 1.2 after a 240-mg dose, indicating no significant accumulation of neratinib after repeated daily dose administration at the dose to be used in this proposed trial. The data indicated a slow distribution of neratinib with a large apparent volume of distribution (Vz/F on day 1: about 3188 to 6181 L) after oral absorption. After oral administration on day 1, neratinib was eliminated with a mean apparent terminal half-life (t½) of approximately 13 to 17 hours. There was moderate to large variability in neratinib t½, Cmax, and AUC; coefficients of Version 02/05/15 Page 13 of 85 variation generally ranged from 8% to 90%.

6.2.2 Form

Neratinib 40-mg tablets will be supplied by the sponsor. There are 210 pills per bottle. Repackaging of product is not allowed. Repackaging of product is allowed, provided site adheres to the following guidances:

- FDA's Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities, and
- USP General Chapter <795> Pharmaceutical Compounding —Nonsterile Preparations

6.2.3 Storage and Stability

Investigational products will be stored by sites in a secure location at the storage conditions listed on the label; store at 25°C (77°F) or below with desiccant (bottle contains the dessicant); do not freeze. Correspondingly, subjects must be instructed to store investigational products in a safe place at these same storage conditions. Storage in a refrigerator or cold room is acceptable as long as the temperature remains above 0 °C. The investigational product must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. The investigational product is only to be administered to subjects who have provided informed consent. Once the investigational product has been assigned to a subject it must not be reassigned to another subject.

6.2.4 Compatibility

There are no known compatibility issues.

6.2.5 Handling

Routine chemotherapy handling is recommended.

6.2.6 Availability

Neratinib is an investigational agent and will be supplied free-of-charge from Puma Biotechnology, Inc.

6.2.7 Preparation

None.

6.2.8 Administration

The number of tablets of neratinib taken will depend on the prescribed dose per the dose administration table. The investigational product will be taken by mouth with food, preferably in the morning. Participants should swallow tablets as a whole and not chew them. Participants should be instructed to take their dose at approximate the same time each day. If the participant forgets to take a neratinib dose more than 3 hours after the intended time, then the dose should be skipped and restarted on the next calendar day. If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be recorded as an adverse event.

6.2.9 Ordering

The agent will be ordered from each institution's individual pharmacy (or designee) using a *Puma Biotechnology* Drug Supply Request Form. This form will be supplied to each institution's pharmacy by the coordinating center once local IRB approval is received. The number of tablets per bottle and the email address to where the form should be sent are detailed on the Drug Supply Request Form. Anticipate 3-5 business days to receive drug after the order is placed.

6.2.10 Accountability

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

6.2.11 Destruction and Return

Neratinib will be destroyed on site according to institutional policies, documented in the Drug Accountability Record Form. At the end of the study, unused supplies of neratinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7. STUDY CALENDAR

Assessment	Screen-ing[a]	Concomitant							Rest[e]	Adjuvant Cycles	End of Tx[g]	30-Day Post Drug[h]	Active Follow-Up[j]	Long Term Follow-Up[j]
		D1[b]	D8[c]	D15[c]	D22[c]	D29[c]	D36[c]	D43-49[d]		D1[f]				
Informed Consent[k]	X													
Medical History[l]	X													
Inclusion/Exclusion Criteria[m]	X													
Vital signs[n]	X	X			X			X		X	X			
Physical Exam	X	X			X			X		X	X			
Neurologic Exam	X	X			X			X		X	X			
Karnofsky Performance Status[o]	X	X			X			X		X	X			
Concomitant Medications[p]	----------X----------													
Adverse Events[q]		----------X----------												
Pregnancy Test (β-HCG)[r]	X	X			X					X	X			
Coagulation[s]	X													
Hematology[t]	X	X	X	X	X	X	X	X	X[dd]	X	X			
Serum Chemistry[u]	X	X			X			X	X[dd]	X[u]	X[u]			
EKG[v]	X									X[v]	X[v]			
ECHO/MUGA[w]										X[w]	X[w]			
Radiation[x]		----------X----------												
Temozolomide		----------X----------												
Neratinib										X				
Imaging – MRI o[y]	X[y]	X[y]								X[y]	X		X	
Response Assessment[z]										X	X		X	
Study Team Contact[aa]										X[aa]				
Post-treatment therapies[bb]													X	X
Survival[cc]													X	X

a. All screening procedures to be performed within 28 days of initial registration. **NOTE: refer to section 10 of master protocol for comprehensive details on screening assessments, initial registration, randomization assignment and second registration timing.**

b. Concomitant radiation and temozolomide must begin no later than 42 days following initial surgery. Day 1 assessments must be performed within 3 days of starting study treatment. Screening assessments may be utilized as baseline/Day 1 assessments if they fall within window.

c. +/- 2 day window for weekly assessments during concomitant phase.

d. Day 43-49 visit to occur within +/- 7 days of completing radiation.

e. Rest period is 28-42 days.
f. Adjuvant C1D1 to begin >28 (+14) days following end of radiation. Cycle 1, Day 1 adjuvant assessments to be performed within 4 days of Day 1 neratinib. All adjuvant cycle 1, day 1 assessments must be resulted and reviewed prior to initiating treatment with neratinib; participants cannot begin adjuvant neratinib if they meet any criteria requiring a dose modification as outlined in section 4.3 of this appendix. **Adjuvant cycles will be 28 days even if treatment is held.** Day 1 assessments for subsequent adjuvant cycles to be performed within 4 days prior to Day 1 neratinib. (If utilizing the assessment window, that does *not* shorten the previous cycle or extend the upcoming cycle; each = 28 days.)
g. End of Treatment: assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment.
h. 30-Day Post Drug: a contact/visit is to be performed 30 days (+7 days) after date of last drug taken on study. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last drug.
i. Active Follow-Up: participants who discontinue study treatment for reasons other than disease progression will be followed every 4 weeks (+/-1 week) via contact or medical record review andstudy team must continue monitoring participant's disease status by radiologic imaging at 8 week intervals (+/- 1 week) until (1) documented disease progression, (2), death, (3) participant withdraws from follow-up, or (4) end of study, whichever occurs first.
j. Long Term Follow-Up: participants will be followed every 4 weeks (+/-1 week) via contact or medical record review until death. Participants must be followed for survival data at every long-term follow-up time point and for post-treatment therapies and reason for stopping those therapies and survival when available.
k. Informed Consent: must be obtained by MD attending. No study specific screening procedures may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration. Following initial registration and receipt of INSIGhT randomization assignment, participants must be sign the consent form specific to the assigned treatment arm prior to initiating treatment for that study arm.
l. Medical History: to include review of treatment history for GBM, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
m. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements for initial registration. See section 2 of this appendix for arm specific eligibility criteria.
n. Vital Signs: weight, heart rate, blood pressure, respiration rate, temperature. Vital signs must be performed prior to administration of treatment on treatment days. Height required only at screening.
o. Karnofsky Performance Status (KPS): see appendix A of master protocol.
p. Concomitant Medications: concomitant medications and reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.
q. Adverse Events: adverse events experienced by participants will be collected and recorded from the first dose of treatment on-study up to the 30-Day Post Drug Visit of the last dose of study medication (+ 7 days depending on when 30-Day Post Drug visit/contact occurs).
r. Pregnancy Test: required for women of child bearing potential (see section 3 of master protocol for definition of women of child bearing potential).
s. Coagulation: PT/INR, PT, PTT required at screening only.
t. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
u. Serum Chemistry: albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed). **In addition, LDH, cholesterol (non-fasting), phosphorus and magnesium are required during adjuvant cycles and End of Treatment chemistry time points.**
v. EKG: required at screening, then within -4 days of C1D1 of adjuvant and within -4 days of day 1 every 3 cycles thereafter (C4D1, C7D1, etc.) during the treatment period. EKG to be performed at End of Treatment visit if one has not been performed within last 12 weeks.
w. ECHO/MUGA: LVEF assessment must be performed within 21 days prior to C1D1 of adjuvant neratinib; an LVEF of ≥50% is required in order for participant to begin treatment with neratinib at adjuvant C1D1. If LVEF is 45-49%, site may reach out to Overall PI via Coordinating Center Team and request prospective approval to proceed with treatment.

LVEF monitoring is not required during treatment unless clinically indicated. ECHO/MUGA to be performed at End of Treatment visit if one has not been performed within previous 12 weeks of date of progression. It is strongly recommended to use the same method of cardiac evaluation (ECHO or MUGA) at each time point for each subject.

x. Radiation: see section 3.1 of this sub-study appendix for definition of standard radiation therapy per protocol.

y. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site, Appendix D Recommended MRI Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial. Local reading (investigator assessment) will be used to determine eligibility and for participant management. Adjuvant C1D1 imaging should be performed within 7 days prior to starting adjuvant treatment; subsequent imaging should be performed within 7 days prior to Day 1 of odd cycles.

z. Response Assessment: Per RANO criteria (see section 11 of master protocol).

aa. Study Team Contact: On day 2, 3 and 4 of adjuvant cycle 1 only, the investigator or designee must contact the participant to inquire about any diarrhea.

bb. Post-treatment Therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected when available.

cc. Survival: date of death and reason must be collected for overall survival purposes.

dd. Hemes & Serum Chemistries will be done as per SOC during patient's post-RT rest phase: hemes = weekly; chemistries need only be performed @ the end of RT visit and prior to adjuvant C1D1 (unless clinically indicated otherwise)

8. MEASUREMENT OF EFFECT

Refer to section 11 of master INSIGhT protocol for details on measurement of effect.

9. REFERENCES

Brennan CW, Verhaak RGW, McKenna A, Campos B, et al. The Somatic Genomic Landscape of Glioblastoma. Cell 2013; 155:462–477.

Ekstrand AJ, Sugawa N, James CD, Collins VP. Amplified and rearranged epidermal growth factor receptor genes in human glioblastomas reveal deletions of sequences encoding portions of the N- and/or C-terminal tails. Proc Natl Acad Sci U S A. 1992 May 15; 89(10):4309-13.

Freedman RA, Gelman RS, Wefel JS, et al. TBCRC 022: Phase II trial of neratinib for patients (Pts) with human epidermal growth factor receptor 2 (HER2+) breast cancer and brain metastases (BCBM). *ASCO Meeting Abstracts.* 2014; 32(15_suppl):528.

Gan HK, Kaye AH, Luwor, RB. The EGFRvIII variant in Glioblastoma Multiforme. J. Clin. Neurosci 2009; 16:748 -754.

Gandhi L, Drappatz, J, Ramaiya NH, Otterson, GA. High-Dose Pemetrexed in Combination with High-Dose Crizotinib for the Treatment of Refractory CNS Metastases in ALK-Rearranged Non–Small-Cell Lung Cancer. J Thoracic Oncology 2013; 8:e3–e5.

Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors**.** Nat Rev Cancer. 2005 May; 5(5):341-54.

Lee JC, Vivanco I, Beroukhim R, et al. Epidermal Growth Factor Receptor Activation in Glioblastoma through Novel Missense Mutations in the Extracellular Domain. PLOS Medicine 2006; 3; 2264-2273.

Libermann TA, Nusbaum HR, Razon N, Kris R, Lax I, et al. Amplification, enhanced expression and possible rearrangement of EGF receptor gene in primary human brain tumours of glial origin. Nature. 1985 Jan 10 18;313(5998):144-7.

Neratinib Graduates to I-SPY 3. *Cancer Discov.* 2014; 4(6):624.

Rabindran SK, Discafani CM, Rosfjord EC, et al. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res 2004; 64(11): 3958-65.

Saura C, Garcia-Saenz JA, Xu B, et al. Safety and efficacy of neratinib in combination with capecitabine in patients with metastatic human epidermal growth factor receptor 2-positive breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014; 32(32):3626-3633.

Vivanco I, Robins HI, Rohle D, et al. Differential sensitivity of glioma- versus lung cancer-specific EGFR mutations to EGFR kinase inhibitors. *Cancer Discov.* 2012; 2(5):458-471.

Wong AJ, Ruppert JM, Bigner SH, Grzeschik CH, Humphrey PA, Bigner DS, Vogelstein B. Structural alterations of the epidermal growth factor receptor gene in human gliomas. Proc Natl Acad Sci U S A. 1992 Apr 1;89(7):2965-9.

Yamazaki H, Fukui Y, Ueyama Y, Tamaoki N, Kawamoto T, et al. Amplification of the structurally and functionally altered epidermal growth factor receptor gene (c-erbB) in human brain tumors. Mol Cell Biol. 1988 Apr;8(4):1816-20.

10. DFCI REPORTABLE AE COVERSHEET – INSIGHT NERATINIB ARM

DF/HCC Protocol No. 16-443

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this AE):

☐ Dr. Patrick Y. Wen and Dana-Farber Coordinating Center
Email: NeuroOnc_SAE@dfci.harvard.edu

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

Participant # and Initials:	
Date Event Met Reporting Criteria (as defined in protocol):	
Type of Report: ☐Initial ☐Follow-up	Hospitalization? ☐ Yes ☐ No

CTCAE Event #1 Description:	CTCAE Event #2 Description (if applicable): *NOTE: use another coversheet if more than 2 events are being reported at this time*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death
Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness to **Temozolomide**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Temozolomide**: ☐Expected ☐Unexpected
Attribution to **Temozolomide**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Temozolomide**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness to **Neratinib**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Neratinib**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Neratinib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Neratinib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Reporting Investigator (print):	

Signature of Reporting Investigator:_____ Date:_____

11. TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Take_____capsule(s) at_____mg strength +_____capsule(s) at_____mg strength

+_____capsule(s) at_____mg strength

This treatment diary is for you to indicate that you took the study drug as prescribed. **Please bring this treatment diary and your pill bottle(s) with you to each clinic visit. At the end of the cycle, please sign and date the bottom of the treatment diary.**

Temodar Instructions

During radiation therapy, **Temodar** should be taken daily (including weekends and holidays) – your Clinical Team will confirm the total # of days you will take Temodar**.**

- Temodar capsules should be taken whole (do not chew or open capsules), two to three hours prior to radiation with a full glass of water on an empty stomach (one hour before or after food and other medications).
- If you realize you have missed a dose by more than 10 hours, the dose should not be retaken and the next dose should not be increased to make up for the missed dose. Please indicate missed doses on this diary.
- If a dose is vomited, the capsules are not to be replaced and you can indicate this vomited dose on the diary.
- On days when you do not have radiation, Temodar should be taken in the morning on an empty stomach (one hour before or after food and other medications) with a full glass of water.
- If your course of radiation extends beyond 42 days because of delays, the course of Temodar may be extended to a maximum of 49 days.

Please check with your study treatment team if you have any questions regarding how or when you should take your Temodar doses.

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 8	**DAY 9**	**DAY 10**	**DAY 11**	**DAY 12**	**DAY 13**	**DAY 14**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 15	**DAY 16**	**DAY 17**	**DAY 18**	**DAY 19**	**DAY 20**	**DAY 21**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Participant/Guardian Signature: _____ Date: _____

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 22	DAY 23	DAY 24	DAY 25	DAY 26	DAY 27	DAY 28
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 29	**DAY 30**	**DAY 31**	**DAY 32**	**DAY 33**	**DAY 34**	**DAY 35**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials
DAY 36	**DAY 37**	**DAY 38**	**DAY 39**	**DAY 40**	**DAY 41**	**DAY 42**
Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: ____ _____ Patient Initials

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Participant/Guardian Signature: _____ Date: _____

TEMOZOLOMIDE DOSING INSTRUCTIONS & DRUG DIARY DURING RADIATION THERAPY

DAY 43	DAY 44	DAY 45	DAY 46	DAY 47	DAY 48	DAY 49
Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials	Date: Temodar Dose:____mg Time of Temodar: _____ _____ Patient Initials

Participant/Guardian Signature:_____ Date: _____

12. NERATINIB DOSING INSTRUCTIONS & DRUG DIARY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Cycle #:_____Month & Year:_____Neratinib Dose:_____mg, once a day

TAKE_____pill(s) daily

Neratinib Description:

- Your study drug (neratinib) is supplied as 40 mg pills

Neratinib Instructions – When and How:

- Take study drug (neratinib) once a day with food, preferably in the morning.
- Take the drug at approximately the same time each day, so that you are taking the drug approximately 24 hours apart.
- Swallow the pills whole; do not chew them or crush them.
- Do not skip any doses.
- If you forget to take your pills at your normal time, you can take your missed dose up to 3 hours after your normally scheduled time. If it has been more than 3 hours, skip the dose and take the next scheduled dose at the usual time the next calendar day. Please call your study nurse or doctor to discuss missed doses.
- If you vomit your pills, write this down in your pill diary. Do not take a replacement dose. Take the next scheduled dose as usual (one dose only). Please call your study nurse or doctor to discuss vomited doses.

Additional Instructions:

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

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

NERATINIB DOSING INSTRUCTIONS & DRUG DIARY

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials
Day 8	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials
Day 15	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials

Participant/Guardian Signature: _____ Date: _____

To be completed by study personnel: Patient ID #_____Patient Initials:_____Month & Year:_____Temodar Dose:_____mg

Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials	Date: No. of pills: _____ Time: _____ _____ Initials

Participant/Guardian Signature:_____ Date: _____

To be completed by study personnel: # of 40 mg Bottles Returned: _____ # of 40 mg Pills Returned: _____

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

Study Personnel Signature: _____ Date: _____

7. ANTIDIARRHEAL DOSING INSTRUCTIONS & DOSING DIARY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Cycle #:_____Month & Year: _____

Prescribed Anti-Diarrheal: _____

This dosing diary is for you to indicate that you took the medication prescribed to you to help prevent diarrhea. It is very important that you take the medication as your doctor tells you to. **Please sign this dosing diary at the end of the cycle and bring the dosing diary back to your next clinic visit.**

- You may experience diarrhea while taking neratinib; therefore, your study doctor will provide you with a prescription for a medication to help prevent diarrhea before you begin neratinib.
- Unless directed by your study doctor otherwise, follow the below instructions **for Cycle 1 only**:
  - Administer loperamide: For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.
  - After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first cycle of therapy (Day 28) from start of neratinib dosing.
  - Thereafter, loperamide will be administered as needed (not to exceed 16 mg per day).
- **After Cycle 1** of neratinib, please defer to your study doctor or nurse for dosing instructions.

If you experience an increase of 4 or more stools a day after beginning neratinib, call your study doctor or nurse as soon as possible.

ANTIDIARRHEAL DOSING DIARY

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Cycle #:_____Month & Year: _____

Prescribed Antidiarrheal: _____

Record the date, time and dose(s) you take each day.

Date	Time	Dose

Date	Time	Dose

Participant/Guardian Signature:_____ Date: _____

To be completed by study personnel:

Patient ID #_____Patient Initials:_____Cycle #:_____Month & Year: _____

Prescribed Antidiarrheal: _____

Record the date, time and dose(s) you take each day.

Date	Time	Dose

Date	Time	Dose

Participant/Guardian Signature:_____ Date: _____

APPENDIX I QBS10072S ARM OF INSIGhT

TABLE OF CONTENTS

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, Quadriga Biosciences, and the IRB for each study site, if appropriate.

1. BACKGROUND

1.1 STUDY DRUG QBS10072S

Rationale & Proposed Biomarker Association

QBS10072S, is a L-type amino acid transporter 1 (LAT-1 targeted alkylating agent associated with extensive and durable DNA damage utilizing LAT1 as both a transport and targeting mechanism. QBS10072S preferentially alkylates DNA at the N7 position of guanine and the N3 position of adenine, resulting in the formation of mono-adducts and intra- and inter-strand crosslinks (ICLs). ICLs distort the DNA double helix and cause the termination of DNA replication and the generation of double strand breaks near the cross-linked site, leading to critical cytotoxic lesions if not repaired [1]. The cytotoxic potential of tertiary bis(2-chloroethyl)amine drugs is much higher than mono-alkylators such as TMZ due to the ability of tertiary bis(2-chloroethyl)amine drugs to form lethal ICLs [2]. The increased potency of tertiary bis(2-chloroethyl)amine drugs may also be due to secondary mechanisms such as inhibition of mitotic checkpoints, inefficient DNA repair, and initiation of p53-dependent DNA-damage stress response, all of which lead to mitotic catastrophe and apoptosis. At least two DNA repair pathways are known to be involved in removal of ICLs: non-homologous DNA end-joining (NHEJ) and Rad51-related homologous recombinational repair (HRR); however, MGMT does not repair damages caused by tertiary bis(2-chloroethyl)amine drugs such as chlorambucil, melphalan, cyclophosphamide, ifosfamide, or DNA chelating agents such as platinum compounds [3]. Therefore, since tertiary bis(2-chloroethyl)amine drugs cross-link, rather than simply methylate DNA as TMZ does, they are more efficacious cytotoxic agents, and cells that are resistant to TMZ are frequently sensitive to tertiary bis(2-chloroethyl)amine drugs. Sensitivity to tertiary bis(2-chloroethyl)amine drugs is cell cycle dependent; thus rapidly proliferating cells such as tumor cells are much more susceptible, while quiescent cells such as the endothelial cells that form the blood-brain barrier (BBB) are not.

Therefore, based on the unique expression of LAT1 on both the BBB and tumor cells and the potent anti-tumor activity of the tertiary bis(2-chloroethyl)amine class of chemotherapeutics, Quadriga has discovered a novel chemical entity (QBS10072S), which combines the molecular characteristics of a selective LAT1 substrate with the validated therapeutic properties of tertiary bis(2-chloroethyl)amine drugs. QBS10072S combines elements necessary for a successful brain tumor treatment: (1) selective transport by LAT1, conferring BBB penetration and uptake into cancer cells, (2) strong tumor cell cytotoxicity using a mechanism distinct from TMZ, and (3) low off-target cytotoxicity in normal brain, BBB, and other systemic organs at therapeutic doses. QBS10072S is a novel BBB permeable compound utilizing a clinically proven alkylating moiety that has the potential to transform the therapy for TMZ-insensitive and relapsed/refractory GBM patients, for whom currently there are no other treatment options.

Most anticancer drugs that are used for systemic tumors are ineffective for treating CNS tumors, in large part due to their inability to cross the BBB and to enter the tumor and peri-tumoral areas at therapeutically meaningful concentrations. The large neutral amino acid transporter type 1 (LAT1) is expressed on both the luminal and abluminal membranes of the microvessels that form the BBB, facilitates uptake of neutral amino acids, such as L-leucine and L-phenylalanine, in a saturable and stereo-selective manner, and has the greatest transport capacity among the BBB amino acid influx transporters [4-6]. LAT1 expression is correlated with tumor progression and poor patient prognosis [7-11]. Quantitative PCR studies have shown a 40- to 400-fold overexpression of LAT1 in GBM compared to normal brain [12]. In gliomas specifically, as the tumor grade and stage increase, LAT1 expression increases in both the tumor cells and at the BBB of the tumor [10]. LAT1 expression in BBB cells in normal tissue adjacent to GBM, while present, is significantly lower than in high-grade glioma cells [10], indicating that LAT1 expression levels in non-cancerous tissues are much lower than GBM. The cytotoxic potential of tertiary bis(2-chloroethyl)amine drugs is much higher than mono-alkylators such as TMZ due to the ability of tertiary bis(2-chloroethyl)amine drugs to form lethal ICLs [2]. Therefore, since tertiary bis(2-chloroethyl)amine drugs cross-link, rather than simply methylate DNA as TMZ does, they are more efficacious cytotoxic agents, and cells that are resistant to TMZ are frequently sensitive to tertiary bis(2-chloroethyl)amine drugs. Sensitivity to tertiary bis(2-chloroethyl)amine drugs is cell cycle dependent; thus rapidly proliferating cells such as tumor cells are much more susceptible, while quiescent cells such as the endothelial cells that form the BBB are not. Therefore, based on the unique expression of LAT1 on both the BBB and tumor cells and the potent anti-tumor activity of the tertiary bis(2-chloroethyl)amine class of chemotherapeutics, QBS10072S combines the molecular characteristics of a selective LAT1 substrate with the validated therapeutic properties of tertiary bis(2-chloroethyl)amine drugs. QBS10072S combines elements necessary for a successful brain tumor treatment: (1) selective transport by LAT1, conferring BBB penetration and uptake into cancer cells, (2) strong tumor cell cytotoxicity using a mechanism distinct from TMZ, and (3) low off-target cytotoxicity in normal brain, BBB, and other systemic organs at therapeutic doses. QBS10072S is a novel BBB permeable compound utilizing a clinically proven alkylating moiety that has the potential to transform the therapy for TMZ-insensitive and relapsed/refractory GBM patients, for whom currently there are no other treatment options.

Clinical Overview

QBS10072S is currently studied in a Phase 1 solid tumor study in Australia. The safety data below is from a data cut on May 31, 2021 (see Investigator Brochure (IB).

It is important to note, however, that most alkylating agents cause gastrointestinal side effects and dose limiting toxicity to bone marrow with the major effect being a decreased granulocyte count. In addition to the effect on the bone marrow, alkylating agents are cytotoxic to mucosal cells resulting in oral mucosal ulceration and effects on the intestinal mucosa. Other organ systems affected by some alkylating agents include the lungs (pulmonary fibrosis) and the liver. The expected DLTs of QBS10072S are bone marrow and gastrointestinal based on GLP toxicology studies. Cardiovascular, respiratory, or neurological toxicities had not been observed in GLP safety pharmacology studies of QBS10072S (see IB).

Nonclinical Overview

In vitro, QBS10072S demonstrated inhibition preference for LAT1 versus the most closely related homologous amino acid transporter, LAT2. QBS10072S inhibited growth and induced apoptosis in various tumor cell lines and demonstrated equivalent cytotoxicity in cells regardless of their MGMT expression status (see Investigator's Brochure: Table 3). Treatment of GBM cells with QBS10072S resulted in a dose-dependent increase in the phosphorylation of H2AX at Ser 139 (γ-H2AX) protein, a DNA damage repair pathway.

In vivo, QBS10072S demonstrated significant tumor growth inhibition in human tumor xenograft models. QBS10072S was effective at suppressing the growth of several tumor types grown both in the flank (melanoma, breast, and prostate cancer) and orthotopically [GBM, acute myeloid leukemia, and myeloma] (see Investigator's Brochure: Table 4).

Using [^{14}C]-QBS10072S, quantitative whole body autoradiography studies in both non-tumor and tumor bearing animals to quantify BBB penetration and brain tumor accumulation were conducted. One hour after administration of 5 mg/kg of [^{14}C]-QBS10072S was dosed IV into a mouse bearing an intracranial GBM tumor (LN229), the tissue concentration of radioactivity was essentially equivalent in the blood and the tumor and significantly lower in the surrounding normal brain tissue, indicating that QBS10072S crossed the BBB and preferentially accumulated within the tumor .

Repeat dose toxicity studies followed by a 4-week recovery period were conducted in Sprague Dawley rats and cynomolgus monkeys. The overall adverse reactions observed in the presence of QBS10072S are generally consistent with the published findings with other alkylating agents, e.g. Evomela® (melphalan HCl).

In the two-cycle (4-week interval between dosing) repeat dose toxicity study in male and female Sprague Dawley rats, QBS10072S was administered (dosing on Day 1 and 29) via 3-minute intravenous infusion at dose levels of 2.5, 5, and 10 mg/kg (male) or 12 mg/kg (female) followed by a 4-week recovery period. The high dose of QBS10072S at 10 mg/kg (male) or 12 mg/kg (female) was not tolerated as most animals in this group were found dead or moribund during Days 5 to 6. Males in the 5 mg/kg group and males/females in 10/12 mg/kg groups were noted with discolored feces, watery feces, crissum staining, food consumption decrease, and/or body weight decrease, while all test article treated animals showed white blood cell (WBC) decrease, reticulocyte (RET) decrease within one week after each dosing, while a recovery trend was noted in the second week. Target organs were defined as hematopoietic immune organs (bone marrow, spleen, thymus, mesenteric lymph node, submandibular lymph node, and Peyer's patch), digestive organs (stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, and submandibular salivary glands), and kidneys. Except for the atrophy in the white pulp of the spleen at ≥5 mg/kg, which showed a recovery trend, all findings above mentioned were completely recovered after four weeks of treatment-free period. All findings were recovered after four weeks of treatment-free period. Based on these findings, the severely toxic dose in 10% of animals (STD_{10}) is considered to be 5 mg/kg for rats.

In the two-cycle (4-week interval between dosing) repeat dose toxicity study in male and female cynomolgus monkeys, QBS10072S was administered (dosing on Day 1 and 29) via 10-minute intravenous infusion at dose levels of 1.25, 2.5, and 5 mg/kg followed by a 4-week recovery period.

The high dose of 5 mg/kg QBS10072S was not tolerated, with decreased activity, nose hemorrhage, inability to rise, hindlimb swelling, hindlimb skin ulcer, and watery feces, while all dose levels showed decreases in WBC, red blood cell (RBC), platelet count (PLT), and RET within two weeks after each dosing, while a recovery trend was noted in the third week post each dose. All findings at dose levels up to 2.5 mg/kg recovered after four weeks of treatment-free period. Target organs were defined as thymus, spleen, lymph node, and bone marrow. Except for the pathological findings at 5 mg/kg, which showed a recovery trend, all findings at dose levels up to 2.5 mg/kg recovered after four weeks of treatment-free period. Based on these findings, the highest non-severely toxic dose (HNSTD) in monkeys is considered to be 2.5 mg/kg.

Per the International Council for Harmonisation (ICH) guideline S9, the highest clinical starting dose for an anticancer small molecule should be equivalent or lower than 1/10 the STD_{10} in rodents or 1/6 the HNSTD in non-rodents. The STD_{10} in rats was considered to be 5 mg/kg based on results of Study No. 18141RD1, and the HNSTD in monkeys was reported to be 2.5 mg/kg in Study No. 18141RD2. These doses correspond to 30 mg/m^2 (K_m = 6 for rat; K_m = 12 for monkey) and provide approximately 10-fold safety margins when compared to the proposed first in human (FIH) dose (3 mg/m^2 for a 60 kg human) (FDA 2005).

QBS100725 was administered to New Zealand White Rabbits in concentrations of 0.5 and 1.0 mg/mL in a vascular and muscular irritation study. In contrast to other alkylating agents, no test article-related irritation reaction was observed in dosing site for both vascular and muscular administration. All findings noted in the vessel, such as thrombus, thrombus organization and perivascular hemorrhage, were incidental and considered to be mechanical stimulation related, thus were not related to QBS10072S

No QBS10072S related hemolysis (in vitro) or irritation (in vivo) was reported in rabbits up to 1 mg/mL. No treatment effects on the CNS or respiratory system in rats after IV administration of QBS10072S by a single 3-minute IV infusion have been observed with a no observed effect level (NOEL) of 8 mg/kg. The human equivalent dose of this, is 16-fold higher than the proposed FIH dose (3 mg/m^2 for a 60 kg human). In a cardiovascular safety study in telemetered monkeys, no statistically significant effect on cardiovascular parameters was observed after IV administration of QBS10072S by a single 10-minute IV infusion with a NOEL of 2.5 mg/kg. The human equivalent dose of this, is 10-fold higher than the proposed FIH dose (3 mg/m^2 for a 60 kg human) (FDA 2005).

Benefit/Risk Assessment

A set of non-GLP and GLP toxicology studies has been performed with QBS10072S. Repeat dose toxicity studies and toxicokinetic evaluation followed by a 4-week recovery period were conducted in Sprague Dawley rats and cynomolgus monkeys. The overall adverse reactions observed in the presence of QBS10072S are generally consistent with the published findings with other alkylating agents, e.g. Evomela® (melphalan HCl). The key potential target organs for QBS10072S include: the bone marrow (e.g. hematological changes) and gastrointestinal tract (e.g., watery feces, weight loss) and skin ulcer, all of which are potentially relevant to humans. Notably for Evomela the warnings and precautions include:

Gastrointestinal toxicity: Nausea, vomiting, diarrhea or oral mucositis may occur; provide supportive care using antiemetic and anti-diarrheal medications as needed.

Anti-Nausea and Anti-Diarrheal Medication: Primary prophylaxis of nausea, vomiting and diarrhea is permitted in the first cycle after discussion with the Sponsor. Primary prophylaxis in subsequent cycles is at the Investigator's discretion. The choice of the prophylactic drug is up to the Investigator (with Sponsor approval) as well as the duration of treatment, assuming there is no known or expected drug-drug interaction.

The most common adverse reactions observed in at least 50% of patients treated with Evomela (melphalan HCl) are neutrophil count decreased, WBC count decreased, lymphocyte count decreased, platelet count decreased, diarrhea, nausea, fatigue, hypokalemia, anemia, and vomiting. The following AEs would be expected with QBS10072S:

Bone Marrow Suppression: Periodic complete blood counts will be monitored, and supportive care will be provided for infections, symptomatic anemia and bleeding until there is adequate hematopoietic recovery

Infection Prophylaxis: Patients, at the discretion of the Investigator, will be given anti-infective agents as needed. Prophylaxis can begin at the time of screening and can continue for up to 1 month post the last QBS10072S administration or longer if CD4 counts are < 200 cells/μL.

Herpes Virus and Epstein Barr Virus: Patients can receive valacyclovir orally or acyclovir intravenously if patient cannot take oral medications.

Pneumocystis: Patients can receive regimens of doses of sulfamethoxazole + trimethoprim as fixed combination beginning at the start of screening. Pentamidine may be substituted in patients with a sulfa allergy.

Fungal: Fluconazole can be initiated and given either orally or as an IV dose. It should be continued until the ANC is > 1000 cell/mm^3.

Gastrointestinal Toxicity: Nausea, vomiting, mucositis, and diarrhea may occur. Use of prophylactic antiemetic medications will be allowed and supportive care will be provided for nausea, vomiting, diarrhea, and mucositis. Including nutritional support and analgesics for patients with severe mucositis.

Hepatotoxicity: Liver chemistries will be monitored, and supportive care provided for symptomatic hepatic disorders including such as hepatitis and jaundice.

Hypersensitivity: Acute hypersensitivity reactions, including anaphylaxis, may occur (e.g. urticaria, pruritus, edema, and skin rashes, tachycardia, bronchospasm, dyspnea, and hypotension.) supportive care will be provided for the reaction and QBS10072S will be discontinued for serious hypersensitivity reactions.

Embryo-Fetal Toxicity: Based on its mechanism of action, QBS10072S: can cause fetal harm when administered to a pregnant woman. Pregnant women will be excluded from this protocol.

Infertility: Based on its mechanism of action, QBS10072S: can cause suppression of ovarian function in premenopausal women resulting in persistent amenorrhea. Based

on its mechanism of action QBS10072S: can cause reversible or irreversible testicular suppression.

Infusion Related Reactions: Infusion reactions may occur with QBS10072S administration. Infusion related reactions are typically characterized by fever, chills (rigor) and less commonly, hypotension. Patients must be pretreated with ondansetron and loratadine approximately 30 minutes prior to the next dose. However, the Investigator should follow institutional practices if the local standard of care is different. All pretreatment and other medications given must be recorded in the patient's eCRF. If infusion-related reactions are observed, it would be recommended to use diphenhydramine as needed, and ondansetron 8mg tid PRN subsequently if needed after infusion for nausea.

Tumor Lysis Syndrome (TLS): TLS occurs when tumor cells release their content in the blood stream, either spontaneously or due to treatment, leading to metabolic disturbances including hyperuricemia, hyperkalemia, hypophosphatemia and hypocalcemia. The incidence and severity of TLS depends on tumor volume, potential for the tumor to lyse and patient characteristics. Preservation of kidney function is most important and management of cardiac and neuromuscular abnormalities. Allopurinol can be used to reduce the hyperuricemia and rasburicase can be used to preserve or improve renal function.

Because hyperkalemia can cause sudden death due to cardiac arrhythmias, patients should limit potassium and phosphorus intake during the TLS risk period (0-3 months).

Frequent measurements of serum electrolytes, continuous cardiac monitoring will occur, and the administration of oral sodium polystyrene will be provided as appropriate. Symptomatic hypocalcemia will be treated with calcium supplementation; non-symptomatic hypocalcemia will not require treatment.

As of the data cut off of May 31, 2021, 9 patients have been treated with QBS10072S; specifically, 2 at 3 mg/m^2, 2 at 6 mg/m2, 3 at 12 mg/m^2 and 2 at 24 mg/m^2, dose levels 1 to 4. The safety profiles of dose levels 1 to 3 were unremarkable with only grade 1, 2 adverse events reported. At dose level 4 1 patient experienced hematologic DLT's and the other patient experienced a fall (not considered related, nor a DLT). These events were reviewed by the cohort review committee and the decision was made to decrease the next dose to 18 mg/m^2 (dose level 5). Dose level 5 is pending enrollment as of May 31, 2021

More detailed information about the known and expected benefits and risks and reasonably expected AEs of QBS10072S may be found in the Investigator's Brochure which is the single reference safety document (SRSD) for this compound.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria Specific to the QBS10072S Arm

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration (section 4 of master protocol). Once the randomization assignment

has been received following initial registration, all participants randomized to the QBS10072S arm must meet the following criteria prior to participating in the QBS10072S arm of the study:

2.1.1 Participants must be willing and able to provide written informed consent/assent for the QBS10072S arm of the INSIGhT trial.

2.1.2 For women of child-bearing potential (women who are not free from menses for > 2years, post hysterectomy/oophorectomy, or surgically sterilized) a negative serum pregnancy test must be documented prior to initial registration. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) from date of initial dose and for 28 days following the last dose of study drug. Men (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in sexual activity with a woman of child-bearing potential from date of initial dose and for 28 days following the last dose of study drug.

2.2 Second INSIGhT Registration: Registration to QBS10072S Arm

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. Registration to the QBS10072S arm must occur following initial registration to master INSIGhT protocol and receipt of randomization assignment, and prior to the initiation of protocol therapy. Any participant not registered to their protocol specific assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria in section 2.1 of this sub-study appendix and a member of the study team will complete the protocol-specific eligibility checklist.

Following initial registration, any additional laboratory assessments prior to start of treatment will not be used to re-confirm eligibility. Refer to section 4 of this appendix for toxicity management between registration and start of study treatment.

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

2.2.1 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

2.2.2 Registration Process for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. The required forms for registration can be found in Appendix B.

Following registration, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Refer to Appendix B, Section 3.7 for registration details.

3. TREATMENT PLAN

Participants treated on the QBS10072S arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix with concomitant QBS10072S administered intravenously. QBS10072S infusion must be done prior to radiation treatment. Radiation must be started no sooner than 2 hours after the end of the QBS10072S infusion, and started no later than 48 hours after the end of the QBS10072S infusion. After a 4-week break following completion of radiation therapy, QBS10072S will be administered once every 28 days. Patients will not receive either concurrent or adjuvant temozolomide. Given the therapeutic hypothesis of radiosensitivity, an initial safety lead-in will be conducted as described in section 3.3 below. The trial will begin with 12 patients registered to the safety lead-in arm. Following the completion of the safety lead-in, the randomized study will begin. Limited pharmcokinetic studies will be performed with the safety lead-in cohort of patients only.

Treatment will continue for a maximum of 7 cycles (one infusion given on Day 1 of Radiation, and for 6 Adjuvant cycles) or development of progressive disease or unacceptable toxicities.

Patients may continue to receive QBS10072S after six adjuvant cycles if they are receiving clinical benefit after agreement between the Investigator and study Primary Investigator.

3.1 Definition of Standard Radiation Therapy

The patient must undergo MRI based treatment planning (CT with contrast-based planning only if patient unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). This volume must be treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast-enhancing region is acceptable. Treatment or no treatment of the T2/FLAIR abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 52 calendar days. Maximum dose (defined as a volume greater than 0.03 cc) to critical structures include: 60 Gy to the brainstem, 56 Gy to the optic chiasm, 55 Gy to the optic nerves, and 50 Gy to the retinae.

Participants are permitted to have radiotherapy as described in this section performed at any NCI funded cooperative group site. Prospective Overall PI approval is required for any radiotherapy site that is not an NCI funded cooperative group site. Any questions regarding permitted

radiotherapy sites should be directed to the DFCI Coordinating Center or Overall PI Patrick Y. Wen, MD.

3.2 Treatment Regimen – QBS10072S Administration

Participants treated on the QBS10072S arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix with concomitant QBS10072S admistered intravenously once during Day 1 of chemoradiation and then every 28 days during the adjuvant period beginning 4 weeks after completion of radiation therapy. Patients will not receive either concurrent or adjuvant temozolomide (all participants have unmethylated MGMT promoter).

The study drug, QBS10072S will be intravenously administered on an outpatient basis.

QBS10072S has not been shown to be either an irritant or vesicant when administered intravenously preclinically. However, this class of medication may cause local tissue damage should extravasation occur. Do not administer by direct injection into a peripheral vein. Administer QBS10072S by injecting slowly (over 60 minutes) into a fast-running IV infusion or via an injection port, or via a central venous line.

QBS10072S should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Identification of the most appropriate cannulation site should be undertaken before insertion. If venous access continually proves difficult, placement of a central venous access device should be considered.

The following are among the conditions of the peripheral cannulation site:

Large veins in the forearm are recommended for peripheral administration.
Cannulation should be avoided over joints.
The inner wrist and the lower extremities should not be used.
Veins in the antecubital fossa or on the dorsum of the hand, particularly for potentially vesicant drugs, are not recommended.
Avoid cannulation where lymphoedema is present.
Cannulation on the side of a mastectomy should be discussed with the Sponsor.

Preventive measures related to the type of peripheral cannula include:

Winged steel infusion devices (‘butterfly’ needles) must not be used for infusion of QBS10072S as the needle can be easily displaced or puncture the venous wall.

Flexible cannula should be used.

Patient related issues where central venous access is highly recommended:

- Small and fragile veins.
- Hard and/or sclerosed veins as a consequence of multiple previous chemotherapy courses or drug abuse.
- Prominent but mobile veins (e.g. elderly persons).

- Known diseases or situations associated with an altered or impaired circulation like Raynaud syndrome, advanced diabetes, severe peripheral vascular disease, lymphedema or superior cava syndrome.
- Predisposition to bleeding, increased vascular permeability or those with coagulation abnormalities.
- Obesity in which peripheral venous access is more difficult.
- Sensory deficits that impair the patient's ability to detect a change in sensation at the site of chemotherapy administration.

Procedures:

a. After cannulation, check for blood flow. Then, flush with 10-ml normal saline and check for signs of extravasation.

Flushing with 10–20 mL of saline solution between different drug infusions is recommended.

A blood return (flashback) should always be obtained before drugs are administered and checked per institutional practice/policy.

Continue monitoring of the cannula insertion site and check regularly for appearance of symptoms such as swelling, pain, or redness sluggish infusion rate.

QBS10072S dosages should be administered concurrently with a fast-running infusion of compatible IV fluid.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded. If a participant requires a QBS10072S dose delay of > 28 days from the next planned dose, the participant must be discontinued from treatment completely. In the exceptional case where the investigator feels the patient would benefit from continuing therapy the case can be discussed with the Overall PI Patrick Y. Wen at pwen@partners.org or 617-632-2166. Expected toxicities and dose reductions and modifications are detailed in section 4 of this appendix.

3.3 Safety Lead-In

Because there is no safety data available for QBS10072S in combination with radiotherapy, a safety lead-in will be conducted utilizing a 3+3 design, including 3-6 patients in each cohort, to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of QBS10072S when administered with radiation therapy. During this part of the study no randomization will occur and all patients will receive QBS10072S. Randomization will begin after the MTD has been determined.

The MTD will be defined as the dose at which ≤ 33% of patients experience a DLT and the MTD/RP2D QBS10072S dose will then be incorporated into the phase II portion of the arm. The first 12 participants enrolled to this arm will be considered as safety lead-in and observed for DLTs for 10 weeks (1 cycle of QBS10072S with 6 weeks of radiation therapy and 4 additional weeks of observation) see ~~section 3.4~~ section 3.5 below for DLT definitions) as follows:

- Treatment will begin at Dose Level 0 (Table 1). Initially 3 participants will be enrolled.
- If none of the 3 participants at a dose level experiences a DLT during the DLT evaluation period (10 weeks), then 3 new participants may be entered at the next higher dose level.
- If 1 of 3 participants experiences a DLT, then 3 more participants will be treated at the same dose level (for a total of 6 subjects in a cohort). If no more than 2 out of 6 participants experience a DLT at that dose, the next higher dose level cohort will be initiated.
- If more than 2 of 6 participants in a given cohort experience a DLT, no further participants will be started at that dose. Three (3) additional participants will be entered at the next lowest dose level if not already complete (6 participants have been enrolled at that dose level).
- If ≤ 1 participant experiences a DLT at the next lowest dose, three (3) additional participants will be entered at that dose level. If no more than 2 out of 6 participants experience a DLT this dose will be the putative MTD.
- Up to an additional 6 participants will be enrolled at the putative MTD for a maximum of 12 patients. Then, if ≤ 4 of the 12 participants treated experience a DLT, this dose will be considered the MTD
- Dose escalation above level 2 or below level -2 will not occur (Table 1). If at Dose Level -2, > 1 of the first 3 participants, > 2 of the first 6 participants, or > 3 of the first 12 participants treated at Dose Level -2 experience a DLT, the appendix will be amended to allow patients to receive radiation therapy with concomitant temozolomide followed by adjuvant single agent QBS10072S.
- An intermediate dose level between the one that leads to a DLT and the immediate lower level may be explored, if appropriate.
    - If > 2 out of 6 patients in the intermediate dose level experience a DLT, no further dose escalation will occur; the MTD would be exceeded, and the next lower dose level may be considered the MTD.
- The study continues until the MTD is declared or the DSMC declares an optimal biologic dose.

The MTD is defined as the highest dose level at which ≤2 of 6 subjects or ≤4 out of 12 participants experience a DLT during the DLT evaluation period. New dose levels may begin accrual only after

all subjects at the current dose level have been treated and observed for a minimum of 10 weeks from the first day of treatment. Toxicity will be graded and recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0). The definition of DLT may be found in Section 3.4.

Table 1: Safety Lead-In QBS10072S Dose Levels in combination with Radiotherapy

Dose Level (DL) *	Dose (mg/m^2)	Maximum percent increase from previous dose
DL-2	3	
DL -1	6	
DL 0**	12	
DL 1	15	33%
DL 2^	18	20%

* The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on safety data and observed systemic exposures
** Starting dose DL 0; de-escalation to a lower dose level (DL -1) may be considered if DLT(s) at the starting dose are observed
^ Any additional dose levels will be increased to a maximum of 33% from the previous dose level.
Note: Prophylaxis for *Pneumocystis jiroveci* pneumonia is recommended during concurrent chemoradiotherapy or if the lymphocyte counts decreased below 500/mm^3.

Table 2: Adjuvant QBS10072S Dose Levels (monotherapy)

Dose Level (DL) *	Dose (mg/m^2)	Maximum percent increase from previous dose
DL -1	6	
DL 0**	12	
DL 1	15	33%
DL 2^	18	20%

* The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on safety data and observed systemic exposures
** Starting dose DL 0; de-escalation to a lower dose level (DL -1) may be considered if DLT(s) at the starting dose are observed
^ Any additional dose levels will be increased to a maximum of 33% from the previous dose level.

After a 4-week break from the last fraction of radiotherapy, patients receive adjuvant QBS10072S every 28 days. The QBS10072S dose will be administered at 12 mg/m^2 for the first cycle, and maybe increased to 15 mg/m^2 at the beginning of the second cycle if no hematological toxicity has occurred.

3.4 Expanded Safety Lead-In

As there was no safety data available for QBS10072S in combination with radiotherapy, a safety lead-in was initially planned utilizing a 3+3 design, including 3-6 patients in each cohort to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of QBS10072S when administered with radiation therapy. Given an absence of DLT during the initial

safety lead-in testing (per section 3.3), an expanded safety lead-in will be conducted to evaluate dose escalation above 18mg/m2 every 4 weeks. For this segment of the study (expanded safety lead-in), randomization will continue to all other open arms and the expanded safety lead-in for QBS10072S.

The MTD_{new} will be defined as the dose at which ≤ 33% of patients experience a DLT and there will be further consideration of evaluating QBS10072S at the MTD_{new} dose after completion of this expanded safety lead-in. For this expanded safety lead-in, patients will be observed for DLTs for 10 weeks (1 cycle of QBS10072S with 6 weeks of radiation therapy and 4 additional weeks of observation) see section 3.5 below for DLT definitions) as follows:

- Treatment will begin at Dose Level 0 (Table 3.4.1 and 3.4.2). Initially 3 participants will be enrolled.
- If none of the 3 participants at a dose level experiences a DLT during the DLT evaluation period (10 weeks), then 3 new participants may be entered at the next higher dose level.
- If 1 of 3 participants experiences a DLT, then 3 more participants will be treated at the same dose level (for a total of 6 subjects in a cohort). If no more than 2 out of 6 participants experience a DLT at that dose, the next higher dose level cohort will be initiated.
- If more than 2 of 6 participants in a given cohort experience a DLT, no further participants will be started at that dose. Three (3) additional participants will be entered at the next lowest dose level if not already complete.
- If ≤ 1 participant experiences a DLT at the next lowest dose, three (3) additional participants will be entered at that dose level. If no more than 2 out of 6 participants experience a DLT, this dose will be the putative MTD_{new}.
- Up to an additional 6 participants will be enrolled at the putative MTD_{new} for a maximum of 12 patients. Then, if ≤ 4 of the 12 participants treated experience a DLT, this dose will be considered the $MTD_{new.}$
- Dose escalation above level 1 or below level -1 will not occur (Table 3.5.1 and 3.5.2). If at Dose Level -1, > 1 of the first 3 participants, > 2 of the first 6 participants, or > 3 of the participants treated at Dose Level -1 experience a DLT, these increased dosing regimens will not be pursued further.
- An intermediate dose level between the one that leads to a DLT and the immediate lower level may be explored, if appropriate.
    - If > 2 out of 6 patients in the intermediate dose level experience a DLT, no further dose escalation will occur; the MTD would be exceeded, and the next lower dose level may be considered the MTD_{new}.
- The study continues until the MTD_{new} is determined.
- The MTD_{new} is defined as the highest dose level at which ≤2 of 6 subjects or ≤ 4 out of 12 participants experience a DLT during the DLT evaluation period. New dose levels may begin accrual only after all subjects at the current dose level have been treated and observed for a minimum of 10 weeks from the first day of treatment. Toxicity will be graded and recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0). The definition of DLT may be found in Section 3.4.

Table 3.4.1: Expanded Safety Lead-In QBS10072S Dose Levels in combination with Radiotherapy

Dose Level (DL) *	Dose (mg/m^2)	Maximum percent increase from previous dose
ESL-DL -1	18	
ESL-DL 0**	21	
ESL-DL 1	21	14%

* The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on safety data and observed systemic exposures
** Starting expanded safety lead-in dose level (ESL-DL 0); de-escalation to a lower dose level (ESL-DL -1) may be considered if DLT(s) at the starting dose are observed
Any additional dose levels will be increased to a maximum of 33% from the previous dose level.
Note: Prophylaxis for *Pneumocystis jiroveci* pneumonia is recommended during concurrent chemoradiotherapy or if the lymphocyte counts decreased below $500/mm^3$. ESL-DL1 is same QBS10072S in combination with radiotherapy but increased frequency during the adjuvant monotherapy phase

Table 3.4.2: Expanded Safety Lead-In Adjuvant QBS10072S Dose Levels (monotherapy)

Dose Level (DL) *	Dose (mg/m^2)	Frequency	Maximum percent increase from previous dose
ESL-DL -1	18	Every 3 weeks	
ESL-DL 0**	21	Every 4 weeks	
ESL-DL 1	21	Every 3 weeks	14%

* The proposed doses, schedule(s), and PK time points may be reconsidered and amended during the study based on safety data and observed systemic exposures
** Starting expanded safety lead-in dose level (ESL-DL 0); de-escalation to a lower dose level (ESL-DL -1) may be considered if DLT(s) at the starting dose are observed
Any additional dose levels will be increased to a maximum of 33% from the previous dose level.

ESL-DL1 is same QBS10072S in combination with radiotherapy but increased frequency during the adjuvant monotherapy phase

After a 4-week break from the last fraction of radiotherapy, patients receive adjuvant QBS10072S every 28 days or 21 days depending on dose level. In the expanded safety lead-in, the QBS10072S dose will be administered at 21 mg/m^2.

3.5 Definition of Dose-Limiting Toxicity (DLT)

A DLT is defined as a clinically significant adverse event considered at least possibly related to QBS10072S and meets any of the criteria below during the first 10 weeks of study treatment (referred to as the initiation/concomitant cycle). If a participant comes off for reasons other than a dose-limiting toxicity during the DLT period, he/she will be replaced.

Dose limiting toxicities are defined below. A DLT must have an attribution of possible, probable, or definite to QBS10072S and meets the below criteria. For patients experiencing a DLT during the safety lead-in portion of the study, QBS10072S must be discontinued. If there is any question concerning a DLT, sites should contact the DFCI Coordinating Center to determine patient's DLT status. The Coordinating Center with the Overall PI will make the final decision.

- Hematological toxicities will be considered dose limiting if any of the following occur (grade 3 or 4 lymphopenia will not be considered a DLT):
    - ANC of $< 500/mm^3$ for > 7 days
    - Platelets $< 25,000/mm^3$ for > 48 hours or platelets $< 50,000/mm^3$ with clinically significant bleeding
    - ≥ Grade 3 febrile neutropenia (ANC $< 1.0 \times 10^9$/L and fever > 101°F/38.3°C)
    - Any hematologic toxicity that prevents administration of QBS10072S for > 28 days
- Non-hematological toxicities will be considered dose limiting if any of the following occur:
    - Inability to complete ≥ 75% of RT due to toxicity related to or exacerbated by QBS10072S added to Radiation Therapy.
    - Grade 3severity, with the following exceptions:
        - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care.Grade 3 hyperglycemia lasting ≤ 4 days (with optimal medical management) and grade 4 hyperglycemia lasting < 12 hours (with optimal medical management)
        - ≥ grade 3 rash of the acneiform or maculopapular type for no more than a 4 day duration (with optimal medical management)
        - Grade 3 electrolyte disturbances that are asymptomatic and that respond to replacement or intervention (e.g. IV fluids) within 48 hours

Dose Limiting Toxicity Definition
Severity of AEs will be graded according to the NCI CTCAE version 5.

3.6 General Concomitant Medication and Supportive Care Guidelines

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

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant are allowed, including drugs given prophylactically (e.g. hematopoietic growth factors, antihistamine, anti-inflammatory agent and antiemetics)

The following medications are permitted at the discretion of the Investigator:

H_2-Receptor Antagonists for symptomatic treatment of gastrointestinal disorder (including, but not limited to famotidine, ranitidine, nizatidine).

Local antacids for symptomatic treatment of gastrointestinal disorder (e.g., aluminum/calcium hydroxide, aluminum/calcium carbonate, bismuth subsalicylate).

Acid reducing agents (including proton pump inhibitors) can be used for symptomatic treatment of gastrointestinal disorder.

5-HT_3 receptor antagonist can be used for the symptomatic treatment of gastrointestinal disorder (including but not limited to ondansetron or granisetron).

The following exceptions are below:

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

3.6.2 Corticosteroids should be used in the smallest possible dose to control symptoms of cerebral edema and mass effect, and discontinued if possible. Prophylactic administration prior to chemotherapy administration will be allowed per standard of care. Acute emergency administration corticosteroids, and acute and chronic topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed. Patients requiring corticosteroids must be on a stable dose for ≥ 5 days prior to each brain MRI assessment.

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

3.6.4 Hematopoietic growth factors: Routine prophylactic use of hematopoietic growth factors is not permitted. However, they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology guidelines.

Please see the clear definition below to remain on study as the ASCO guidelines which are referred to as a source have a disclaimer that the information provided should not be relied upon as being complete and accurate:

- Patients experiencing Grade 3 or 4 potentially treatment-related toxicity or intolerable Grade 2 toxicity despite supportive care should have their treatment interrupted/delayed. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.
- treatment delay or interruption of more than 28 days due to lack of recovery will result in discontinuation of the patient from treatment unless there is clinical benefit, and this is discussed with the Sponsor. A dose of study treatment may be given only if:
    - ANC ≥1,000/mm3.
    - Platelet count ≥75,000/ mm3.
    - Non hematologic toxicities have returned to baseline or Grade ≤1 severity (except for alopecia, nausea, and vomiting) or, at the Investigator discretion,

Grade ≤2 if not considered a safety risk for the patient.

- If these conditions are not met, treatment must be delayed by 1 week. If, after a 1 week delay, all toxicities have recovered within the limits described above, treatment with QBS10072S can be resumed. If the patient has not recovered after 1 week of delay, treatment may be delayed by 2 more weeks. However, initiation of the next cycle can only be delayed by a maximum of 3 weeks. Therefore, if persisting toxicity does not allow QBS10072S treatment resumption within 49 days of Day 1 of the previous cycle (for the Q4W dosing regimen), treatment with QBS10072S will be permanently discontinued. A patient may continue on study after discussion with the Sponsor if there is documentation of clinical benefit following recovery of the AE to Grade 0 1 or baseline, only after discussion between the Investigator and Sponsor.

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

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

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

3.6.8 Surgery: If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the operative note, and pathology report. Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and QBS10072S required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping QBS10072S is recommended at least 28 days prior to surgery. Postoperatively, the decision to reinitiate QBS10072S treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

3.6.9 Other anticancer or experimental therapies: No other anticancer therapy of any kind is permitted during the study treatment period. No other drug under investigation may be used concomitantly with the study drug.

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

3.6.11 QBS10072S related mucositis and mouth ulcers should be treated as early as possible and according to institutional standard medical practice. This may include analgesics, topical preparations (suspensions, pastes), and short courses of systemic steroids with temporary dose interruption and/or dose reduction for more severe cases. Alcohol or peroxide-containing mouthwashes should be avoided.

3.6.12 Infections (including the SAEs of pneumonia, sepsis, and nonserious AEs of infection) and associated pyrexia were reported with QBS10072S. Vigilance for the signs and symptoms of infection should be practiced with subjects receiving treatment with QBS10072S and managed according to institutional standard medical practice. Routine infectious disease prophylaxis is not recommended; however, antibiotic, antiviral, anti-pneumocystis, antifungal, or other prophylaxis may be implemented during the study at the discretion of the investigator.

3.7 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue on the QBS10072S arm until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the every 28 day intravenous medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

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

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Patrick Y. Wen, MD, at 617-632-2166 or pwen@partners.org.

3.8 Duration of Follow Up

Participants will be followed until death with monthly visits, telephone contact, or medical record review. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Refer to section 7 study calendar within this appendix for follow-up requirements and time points.

3.9 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

4. DOSING DELAYS/DOSE MODIFICATIONS

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug. If administration of QBS10072S must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in this section.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

The occurrence of any Grade 5 event or any two Grade 4 events considered at least possibly related to QBS10072S and unexpected with QBS10072S will trigger suspension of accrual and performance of a thorough safety review prior to resuming enrollment.

4.1 Anticipated Toxicities

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

4.1.1 Anticipated Toxicities for Radiation Therapy

A list of adverse events of all grades suspected to be radiation therapy treatment related, organized by CTCAE v5.0 category, includes:

- EAR AND LABYRINTH DISORDERS – external ear inflammation; other: dryness of ear canal; other: hardening of ear canal wax; external ear pain; other: hearing loss
- ENDOCRINE DISORDERS - other: hypophysitis, or hypopituitarism
- EYE DISORDERS – cataract; other: decreased vision
- GASTROINTESTINAL DISORDERS – nausea; vomiting
- GENERAL DISORDERS – fatigue
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – injury other: optic nerve
- INVESTIGATIONS –lymphocyte count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness
- NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED – treatment related secondary malignancy
- NERVOUS SYSTEM DISORDERS – headache; seizure; memory impairment; cognitive disturbance; somnolence; dysgeusia; central nervous system necrosis
- PSYCHIATRIC DISORDERS – personality change
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – scalp pain; other: scalp redness; alopecia

4.1.2 Suspected & Anticipated Toxicities for QBS10072S

A list of adverse events of all grades suspected to be QBS10072S treatment related according to review of Investigator's Brochure, potential for **cross-sensitivity** between other alkylating agents, and class effect toxicities and preclinical data, examples include:

Bendamustine Adverse Events of Interest and Safety Considerations [refer to Package insert]

- Hepatic Impairment: Use not recommended in patients with moderate or severe hepatic impairment.
- Renal Impairment: Use not recommended in patients with severe renal impairment.
- Infusion Reactions and Anaphylaxis: Infusion reactions (e.g., fever, chills, pruritus, rash) occur commonly. Severe anaphylactic and anaphylactoid reactions reported rarely, mainly in the second and subsequent cycles of therapy.
- Risk of severe (grade 3 or 4) and potentially fatal myelosuppression, manifested primarily as lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia. Neutropenic sepsis, diffuse alveolar hemorrhage, and cytomegalovirus (CMV) pneumonia reported.
- Infections (e.g., pneumonia, sepsis, hepatitis) resulting in septic shock and death have occurred in adults and pediatric patients. Increased risk of infection in patients with myelosuppression.
- Increased risk of reactivation of infections (e.g., HBV infection, CMV infection, tuberculosis, herpes zoster).
- Tumor lysis syndrome reported, generally during the first cycle of therapy; without appropriate intervention, acute renal failure and death may occur.
- Possible dermatologic reactions (e.g., rash, toxic skin reactions [Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms {DRESS}], bullous exanthema); may be progressive and increase in severity with continued therapy.
- Liver injury, sometimes fatal or serious, reported, although confounding factors (e.g., concomitant use of other antineoplastic agents, progressive disease, reactivation of HBV) reported in some cases. Generally occurs during initial 3 months of therapy.
- Development of premalignant (e.g., myelodysplastic syndrome, myeloproliferative disorders) and malignant diseases (e.g., acute myelogenous leukemia, bronchial carcinoma) reported.
- Extravasation may cause pain, erythema, and marked swelling and may result in hospitalization. Monitor infusion site for erythema, swelling, pain, infection, and necrosis during and after administration of bendamustine.
- May cause fetal harm; increased resorptions, skeletal and visceral malformations, and decreased fetal body weights demonstrated in animals.
- Avoid pregnancy during and for 3 months after discontinuance of therapy. If used during pregnancy or patient becomes pregnant, apprise of potential fetal hazard. Advise men with partners of childbearing potential to use a reliable method of contraception during and for 3 months after discontinuance of therapy.

Chlorambucil Adverse Events of Interest and Safety Considerations [refer to package insert]

- Possible leukemia or secondary malignancies; assess risk/benefits of therapy.

- May cause fetal harm (e.g., unilateral renal agenesis); avoid pregnancy during therapy. If used during pregnancy or if patient becomes pregnant, apprise of potential fetal hazard.
- High incidence of sterility (generally irreversible) in prepubertal and pubertal males; potential for prolonged or permanent azoospermia in adult males.
- Amenorrhea reported in females.
- Possible angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and urticaria.
- Potential for cross-sensitivity (rash) between chlorambucil and other alkylating agents.
- Slowly progressive lymphopenia is common; return to normal lymphocyte counts generally occurs rapidly after completion of therapy.
- Possible dose-dependent, reversible neutropenia after third week of continuous therapy and continuing for up to 10 days after last dose.
- Risk of irreversible bone marrow damage increases rapidly with total dose ≥6.5 mg/kg in 1 course of continuous dosing regimen.
- Note: Adverse hematologic effects may be less severe with intermittent dosing than with continuous dosing.
- Possible increased risk of seizures in children with nephrotic syndrome and patients receiving high pulse doses of chlorambucil.
- Possible additive myelosuppressive effects; do not administer at full dosages within 4 weeks after a full course of radiation therapy or myelosuppressive drugs.
- Immunization: Avoid administration of live vaccines to immunocompromised patients.

Melphalan Adverse Events of Interest and Safety Considerations [refer to package insert]

- Renal Impairment: In patients with renal impairment (BUN ≥30 mg/dL), reduce dosage by 50%.
- Risk of dose-limiting myelosuppression, manifested principally by leukopenia and thrombocytopenia; anemia also may occur.
- Leukocyte and platelet nadirs generally occur 2–3 weeks after treatment; recovery usually occurs 4–5 weeks after treatment. Irreversible bone marrow depression has been reported.
- Positive direct Coombs' test results and concurrent hemolytic anemia have been reported.
- Use with caution in patients with compromised bone marrow reserve (i.e., prior radiation therapy or prior therapy with other cytotoxic agents.
- Possible leukemia or secondary malignancies.
- May cause fetal harm; teratogenicity and embryolethality demonstrated in animals. Avoid pregnancy during therapy. If used during pregnancy or patient becomes pregnant, apprise of potential fetal hazard. Pregnancy Category D. Melphalan may cause fetal harm when administered to a pregnant woman. While adequate animal studies have not been conducted with IV melphalan, oral (6 to 18 mg/m2/day for 10 days) and IP (18 mg/m2) administration in rats was embryolethal and teratogenic. Malformations resulting from melphalan included alterations of the brain (underdevelopment, deformation, meningocele, and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as hepatocele (exomphaly). There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to

the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

- Reversible and irreversible testicular suppression reported.
- Ovarian suppression and amenorrhea reported in premenopausal females.
- Extravasation may produce severe local tissue necrosis.
- Hypersensitivity reactions, including anaphylaxis, urticaria, pruritus, edema, rashes, tachycardia, bronchospasm, dyspnea, and hypotension reported in 2% of patients receiving IV melphalan and rarely in patients receiving oral melphalan.
- Potential for cross-sensitivity (rash) between melphalan and other alkylating agents.
- Avoid administration of live vaccines to immunocompromised patients.
- Pulmonary embolism sometimes fatal and fibrosis have been reported.
- Increased bone marrow suppression and risk of severe leukopenia in patients with renal impairment receiving IV melphalan; dosage reduction should be considered.

4.2 Dose Modifications/Delays for QBS10072S

4.2.1 Table 4.2 should be adhered to for all toxicities considered at least possibly related to QBS10072S. If a participant experiences a toxicity unlikely or unrelated to treatment with QBS10072S but may still warrant a hold or reduction of study drug for safety, discussion and approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD, is strongly recommended.

4.2.2 When treatment must be held pending resolution of toxicity to grade 1 or return to baseline, and the toxicity is a lab abnormality (**with the exception of thrombocytopenia and neutropenia**) in cases where participant had a pre-existing laboratory abnormality at baseline, the toxicity can be considered "resolved" from a hold perspective when it has resolved to within 1 grade of the baseline value. **For thrombocytopenia and neutropenia please refer to Table 4.2.**

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

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

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

4.2.4 No more than 2 levels of dose reduction are permitted in this study. Participants cannot be treated below dose level -2. If a participant whose QBS10072S dose has been reduced by 2 dose levels requires another dose reduction, treatment on study must be stopped unless the participant has benefited from the study, in which case the investigator will contact the overall Principal Investigator, Dr. Patrick Y. Wen, to determine if the participant will remain in the study.

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

4.2.6 No dose re-escalation is permitted on study.

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

4.2.8 Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 4.2, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events for 30 days following the last dose of QBS10072S. All SAEs must be reported as detailed in section 5.3 of this appendix.

Table 4.2: Criteria for dose-modification and re-initiation of QBS10072S treatment

Table 4.2 should be adhered to for all toxicities attributable (considered at least possibly related) to QBS10072S as noted below. If a participant experiences a toxicity unlikely or unrelated to treatment with QBS10072S but may still warrant a hold or reduction of study drug for safety, discussion and written approval by Overall Principal Investigator and Study Sponsor, Patrick Y. Wen, MD is strongly recommended.

Event	Action
Serum bilirubin ≥2 x ULN or other Grade 3 or Grade 4 nonhematologic toxicity considered at least possibly related to QBS10072S per Investigator judgment (including persistent nausea, vomiting, diarrhea despite optimal medical therapy) **Bilirubin** (for patients with Gilbert Syndrome* these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated	Hold QBS10072S infusion until recovery to Grade 0-1, serum bilirubin < 2 xULN or baseline and reduce by 1 dose level. Discontinue QBS10072S if dose delay is more than 3 weeks*. If toxicity reoccurs despite reduction, patient may be dose reduced again by another dose level upon recovery to Grade 0-1 or baseline unless the patient is in the first dose group, then only 1 dose reduction is allowed. Prompt palliative measures are strongly encouraged (e.g., anti-emetics). Patients who experience Grade 4 nonhematologic toxicities despite optimal medical intervention should be discontinued from the study*. * For participants with Gilbert's syndrome prior to registration, the clinician may choose to continue QBS10072S for elevations in total bilirubin that are two times the participant's baseline value (screening value). For total bilirubin that is greater than two times the baseline value, follow dose modification guidelines as outlined in the above table. However, in place of resolution to ≤ grade 1, QBS10072S may resume once resolution to ≤ 2 x baseline value.

Event	Action
Hematologic toxicity considered at least possibly related to QBS10072S per Investigator judgment Grade 4 neutropenia, i.e., ANC <500/mm^3 (0.5 x 10^9/L) for more than 7 days. Febrile neutropenia, i.e., fever with a single temp >38.3°C or sustained temp ≥38°C for more than 1 hour with ANC <1000/mm^3.	Hold QBS10072S until recovery of ANC to ≥1.0 x 10^9/L (1,000 cells/mm^3) Reduce QBS10072S by 1 dose level. If toxicity reoccurs despite dose reduction, patient may either be held until recovery and continuation at same dose or undergo further dose reduction by another dose level unless the patient is in the first dose group, then only 1 dose reduction is allowed.
Thrombocytopenia Grade 4 thrombocytopenia, i.e., PLTS <25,000/mm^3 (25.0 x 10^9/L). Or Grade 3 thrombocytopenia with clinically significant or life-threatening bleeding.	Hold QBS10072S until platelets ≥100,000/mm^3. For platelet counts 10,000 – 25,000/mm^3, continue monitoring every 3 days until recovery to ≥25,000/mm^3 (Grade 3 or less). For platelet counts ≤10,000/mm^3 monitor daily until recovery to ≥25,000/mm^3 (Grade 3 or less). Reduce QBS10072S by 1 dose level. If toxicity reoccurs despite dose reduction, patient may either be held until recovery and continuation at same dose or undergo further dose reduction by another dose level unless the patient is in the first dose group, then only 1 dose reduction is allowed. Discontinue for life-threatening bleeding.
Other Grade 4 hematologic toxicity despite medical therapy considered at least possibly related to QBS10072S and clinically significant per Investigator's judgment	Hold QBS10072S until recovery to Grade 0-1 or baseline and reduce QBS10072S dose by 1 dose level. If toxicity reoccurs despite dose reduction, patient may either be held until recovery and continuation at same dose or undergo further dose reduction by another dose level unless the patient is in the first dose group, then only 1 dose reduction is allowed.
No recovery of toxicities within 3 weeks of scheduled QBS10072S infusion	Discontinue treatment.*
Other unspecified Grade 1 and 2 events considered at least possibly related to QBS10072S	Maintain treatment with QBS10072S
Other unspecified Grade 3 clinically significant events considered at least possibly related to QBS10072S	Interrupt treatment until resolution to ≤ grade 1 or returned to baseline, treatment may resume at the same dose level or a 1 dose level decrease, at the investigator's discretion. Continuation of QBS10072S is permitted upon recovery to stable Grade 2 if the investigator and overall principal investigator (Dr. Patrick Y. Wen) agree that the event is not considered clinically significant
Other unspecified Grade 4 events considered at least possibly related to QBS10072S	Discontinue QBS10072S

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (section 4.1 of this appendix) and the characteristics of an observed AE (section 5.2 of this appendix) will determine whether the event requires expedited reporting **in addition** to routine reporting.

This section specifies reporting requirements to the FDA, Overall PI/Coordinating Center, DF/HCC IRB, and manufacturer as applicable.

5.1 Expected Toxicities

Refer to section 4.1 of this appendix for expected toxicities for assigned study treatment arm.

5.2 Adverse Event Characteristics

- **Adverse Event (AE) Definition:**
  An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

  Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized or determined to be irreversible by an investigator.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in section 4.1 of this appendix should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the

next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

- **Serious Adverse Event (SAE) Definition**:
  A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:
  - Results in death
  - Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
  - Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
  - Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
  - Is a congenital anomaly/birth defect;
  - Constitutes an important medical event. Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

5.3 Expedited Adverse Event Reporting

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

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event that is *Serious, Unexpected,* and there is a *Reasonable Possibility* (i.e., possible, probable, or definitive attribution) the Adverse Event is related to the study intervention.

Expedited Reporting Guidelines to Overall PI/Coordinating Center & Quadriga Biosciences

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites outside of DF/HCC will report AEs to their respective IRB according to

the local IRB's policies and procedures in reporting adverse events. A copy of the AE form should be forwarded to the Overall PI within the timeframes detailed in the table below. The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to the DFCI IRB policies and procedures in reporting adverse events.

In addition to local IRB reporting policies, all sites are required to follow the Table 5.3.3 expedited reportable AE requirements:

Table 5.3.3 Expedited AE Reporting Requirements to Quadriga Biosciences Company & DFCI Coordinating Center

Adverse Event Characteristics				Reporting Requirement	
Serious-ness	**Toxicity**	**Known Correlation[f]**	**Attribution to QBS10072S**	**Quadriga Biosciences- Via Fax or email[c] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**	**Overall PI (Patrick Y. Wen, MD) at the DFCI Coordinating Center Via Email [b] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**
Serious[e]	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [a]	Within 24 hours from notification [a]
Non-Serious	Grade 4	Any (Expected or Unexpected)	Any	Not Required	Within 5 working days from notification [a]
Non-Serious	Grade 2 or 3	Unexpected	Possible, probable, definite	Not Required	Within 7 working days from notification [a]

a. In the event that the participating investigator/site team does not become aware of an adverse event requiring expedited reporting immediately (e.g., participant sought treatment elsewhere), the participating investigator/site team is to report the event within the required hours/days noted above after learning of it and document the time of his or her first awareness of the adverse event. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE or reportable AE is required.

b. Email the Medwatch 3500A form, reportable AE coversheet (section 10 of this appendix), and the local IRB SAE report (if applicable) to the DFCI Coordinating Center with the subject title as "INSIGHT SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Patrick Y. Wen, and to the DFCI Coordinating Center personnel.

c. Reportable AE Coversheet is found in section 10 of this appendix. The coversheet contains all FAX numbers/e-mails and needed for reporting purposes.

d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm

e. Seriousness is defined in section 5.2 of this appendix.

f. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Anticipated Toxicities list (protocol section 4.1 of this appendix) which is derived from the Investigator's Brochure.

How to report expedited AEs to Quadriga Biosciences & DFCI Coordinating Center/Overall PI

1. Document/describe reportable AE(s) on the following:
    a. MedWatch 3500A
        i. Downloadable form at http://www.fda.gov/medwatch/getforms.htm
    b. DFCI Reportable AE Coversheet – INSIGhT QBS10072S Arm
        i. Coversheet can be found in section 10 of this appendix. The coversheet contains contact information for DFCI Coordinating Center and Quadriga Biosciences safety groups. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.
2. Scan and email above documents to NeuroOnc_SAE@dfci.harvard.edu with the subject title "INSIGHT SAE"
    a. All AE reports received at this account are forwarded immediately to Overall Principal Investigator (Dr. Patrick Y. Wen), and to Coordinating Center personnel.
    b. If available and applicable, also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.

Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

- Lymphopenia (grades 2-4).
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status *(e.g. routine colonoscopy)*
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for treatment of patient's underlying disease after coming off study treatment *(e.g. admission after patient is removed from active study treatment for craniotomy)*

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

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

5.5 Expedited Reporting to Hospital Risk Management

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

5.6 Routine Adverse Event Reporting

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

5.7 Other Reporting Requirements

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) in either a female subject or a partner of a male subject occurring while the subject is on investigational product (IP), or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately if the female subject becomes pregnant, if the partner of a male subject pregnant study continuation must be discussed with the primary investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the DFCI Coordinating Center and Overall PI (Dr. Patrick Wen) and to Quadriga Biosciences Drug Safety within 24 hours from notification using the DFCI Reportable AE Coversheet (INSIGhT QBS10072S arm). If the female partner of male participant becomes pregnant report will be made after obtaining the necessary signed informed consent from the female partner.

The female may be referred to her obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify the DFCI Coordinating Center and Overall PI (Dr. Patrick Wen) and Quadriga Biosciences Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the DFCI Reportable AE Coversheet (INSIGhT QBS10072S arm) as a follow-up to the initial pregnancy report.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus must be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus], ectopic pregnancy), the Investigator should report the abnormal outcome as a SAE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to the DFCI Coordinating Center and Overall PI (Dr. Patrick Wen) and Quadriga Biosciences Drug Safety within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to the DFCI Coordinating Center and Overall PI (Dr. Patrick Wen) and Quadriga Biosciences Drug Safety within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the DFCI Coordinating Center and Overall PI (Dr. Patrick Wen) and Quadriga Biosciences Drug Safety within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form. While the investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Overdose

Overdose, as defined for this protocol, refers to QBS10072S dosing only.

On a per dose basis, an overdose is defined as a dose of QBS10072S at any amount over the protocol-specified dose assigned to a given patient, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Notify the DFCI Coordinating Center at NeuroOnc_SAE@dfci.harvard.edu of any potential overdose as soon as possible.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Quadriga Biosciences as a supporter of this study as follows:

Quadriga BioSciences, Inc.
339 S. San Antonio Road, Suite 2A
Los Altos, CA 94022
Tel: (908) 673-9000

6. PHARMACOKINETICS

6.1 Blood Collection for Pharmacokinetic Analysis

Blood samples of approximately 3 mL each will be collected over a 24-hour period at specified time point predose (within 60 min prior to the start of IV infusion) and postdose as delineated in Table 6 for PK analysis, which will allow assessment of systemic exposures, accumulation and other PK properties of QBS10072S.

The actual date and time (24-hour clock time) of each sample will be recorded. It is essential that the actual date and time of study treatment administration and sample collection be recorded in the eCRF. Nominal PK blood sampling times and collection windows should be adhered to as closely as possible, in accordance with Table 6.1. Plasma concentration data will be used to determine PK parameters, including AUC0-t, AUCinf, Cmax, Cmin, Tmax, and t½, in all subjects during Cycle 1 and Cycle 2, if applicable, and if data are evaluable. Metabolites of QBS10072S may be investigated if applicable.

During the course of the study, as data emerge and enhance the understanding of QBS10072S PK, PK sampling occasion days and collection times may be modified.

To avoid contamination of PK samples with infusion solution, blood samples for PK should be collected from the contralateral arm.

Table 6.1: Plasma Collection Schedule for Pharmacokinetic Analysis For Safety Lead-In:

Study Day	Sample Times
Concomitant/Initiation C1D1	Predose, at 15 minutes (±5 m), 30 minutes (±5 m)* **post start of infusion,** End of Infusion (within 2m prior to EOI), and 5 minutes (+10 m), 30 minutes (± 5 m), 1 hour (± 5 m), 2 hours (± 5 m), 3 hours (± 10 m), 5 hours (± 10 m), 7hours (± 20 m) **post end of Infusion**
Concomitant/Initiation C1D2	24 hours (±1.0 hour) after C1D1 dose
Adjuvant C1D1	Predose, at 15 minutes (±5 m), 30 minutes (±5 m)* **post start of infusion,** End of Infusion (within 2m prior to EOI), and 5 minutes (+10 m), 30 minutes (± 5 m), 1 hour (± 5 m), 2 hours (± 5 m), 3 hours (± 10 m) **post end of Infusion**

6.2 Pharmacokinetic Analyses

Plasma QBS10072S concentrations and actual blood sampling times will be listed by dose level and protocol specified assessment time point. They will be summarized using descriptive statistics - number of measurements, arithmetic mean, SD, and % CV, geometric mean, minimum, median, and maximum for each dose level at each scheduled assessment time point. Individual and mean concentration-time profiles will be presented graphically for each treatment. Pharmacokinetic parameters will be computed from the individual plasma concentrations using a non-compartmental approach and will be summarized by treatment using descriptive statistics.

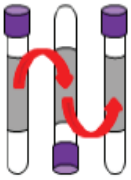
6.3 **Pharmacokinetic Collection and Processing**

Labels, purple top and microtubes (containing HCL) will be supplied by the lab.

Storage will be -70C or below.

Shipping will be on dry ice.

Please follow the **Procedure for PK Plasma Collection and Processing** instructions located in the Laboratory Manual under section 5.1.

Test	Draw Tube	Mix by Inversion	Processing	Transport or Aliquot	Shipping temperature, destination
Plasma	K_2EDTA 4.0 mL 	Gently invert 8-10times 	Fill ***K_2EDTA tube*** completely. Following blood collection, the samples should be placed *immediately* on wet ice pending centrifugation. **Centrifugation should be performed within 30 minutes of sample collection**. Centrifuge at 2-8 °C for at least 10 minutes at 1500 x *g* to obtain plasma. **Keep plasma on wet ice after centrifugation.** Transfer plasma into the pre-chilled transfer tube containing 40 uL of 5N HCl for every 800 uL of plasma (for example, add 120uL of 5N HCl in 2.4mL of plasma). Invert 8-10 times to mix. Withdraw the plasma and aliquot **all plasma** into 3 pre-labeled cryovials. (each containing at least 0.5 mL, and the last containing all the remaining plasma). Invert the tubes 6-8 times. Plasma should be frozen at -70°C within 30 minutes of centrifugation for storage or packed immediately on dry ice for shipment. If plasma volume is low, ensure that aliquot 1 (primary) and aliquot 2 (primary) contain at least 0.5 mL and use the remaining plasma for aliquot 3 (back-up).	Plasma Transport tube  Cryovial x 3, 0.5 mL each (minimum) 	Frozen on dry ice. **FedEx Priority Overnight** Mon-Thurs Ship to Alliance Pharma

7. PHARMACEUTICAL INFORMATION

QBS10072S

7.1.1 Description

The chemical name for QBS10072S is (S)-3-Amino-4-[5-[bis(2-chloroethyl)amino]-2-methyl-phenyl]butanoic acid.. QBS10072Sis also has an empirical formula of $C_{15}H_{22}Cl_2N_2O_2$ and a molecular weight of 333.25 g/mol.

Pharmacokinetic data for QBS10072S are summarized in the IB. QBS10072S has a short half-life of 0.60 – 0.79 h at dose levels of 0.5 – 3.0 mg/kg in monkeys and 0.74 – 0.90 h at dose levels of 0.5 – 4.5 mg/kg in rats, respectively. Presumably, QBS10072S undergoes rapid hydrolysis *in vivo* as in the case of bendamustine to form QBS10150S which is further hydrolyzed to form the bis(2-hydroxyethyl)amine product (i.e., QBS10151S). The rat PK parameters for QBS10072S and QBS100150S were determined. Specifically, the overall $\%AUC_{QBS10150S/QBS10072S}$ was 8.80% and 9.28% for female rats and male rats, respectively, indicating that a far greater percentage of QBS10072S is hydrolyzed *in vivo* than the percentage of QBS10150S present in both drug substance (DS) and DP.

7.1.2 Form

QBS10072S for injection is supplied as a sterile white to off-white lyophilized powder in a single-dose vial for intravenous use. Each vial contains 50 mg QBS10072S free base and 2700 mg Betadex Sulfobutyl Ether Sodium, NF. The lyophilized powder with excipient will be reconstituted with 0.9% Sodium Chloride Injection, USP to a concentration of 50 mg/10 mL (5 mg/mL). The resulting solution will be further diluted to 0.5 mg/mL for intravenous infusion.

7.1.3 Storage and Stability

QBS10072S vials are to be stored at 2 to 8° C.

Personnel involved with the study should be aware of the location of study drug storage. All study drug is to be stored in a secured area and accessible only to appropriate study personnel.

A daily temperature log must be maintained by the site.

The reconstituted solution (5 mg/mL) is stable for 24 hours at refrigerated temperature (2 to 8°C) and for 2 hours at room temperature (20 to 25°C).

QBS10072S reconstituted solution (5 mg/mL) is to be stored at 2 to 8°C temperature if not to be used immediately for admixture preparation and it must be allowed to reach room temperature for 15 minutes prior to use.

The admixture solution (0.5 mg/mL) is stable for 4 hours at room temperature in addition to 8 hours at refrigerated temperature (2 to 8°C) following dilution, refers to the following table.

QBS10072S admixture solution (0.5 mg/mL) is to be stored at 2 to 8°C temperature if not to be used immediately and it must be allowed to reach room temperature for 15 minutes prior to use.

Infusion must be completed within 4 hours from taking the admixture solution out of the refrigerated condition.

Stability of QBS10072S reconstituted solution (5 mg/mL) and admixture solution (0.5 mg/mL)

Name	Container	Storage condition	
		2 to 8 °C	Room temperature
Reconstituted solution (5 mg/mL)	Original Vial	NMT* 24 hours	NMT* 2 hour
Admixture solution (0.5 mg/mL)	Terumo Syringe	NMT* 8 hours	NMT* 4 hours
	Baxter Viaflex Infusion Bag		

Note: The combined storage time of the reconstituted solution (5mg/ml) and the admixture solution (0.5 mg/mL) for the diluted drug product must not exceed 4 hours at room temperature or 24 hours under refrigerated conditions

***NMT- No More Than**

Cold-chain monitoring is required for any drug product that is transferred to refrigerated storage prior to administration.

7.1.4 Compatibility

QBS10072S should be diluted in saline (0.9% Sodium Chloride Injection, USP). Do not mix QBS10072S with other injectable drug products.

7.1.5 Handling

QBS10072S is a cytotoxic drug and applicable special handling and disposal procedures must be followed.

7.1.6 Availability

QBS10072S is an investigational agent and will be supplied free-of-charge from Quadriga Biosciences.

7.1.7 Dose Preparation

Once the Investigator has confirmed all inclusion/exclusion criteria have been met and the Sponsor has approved enrolment of the patient, a completed prescription form will be signed by the Investigator and provided to the Pharmacy.

The prescription should be prepared in compliance with institution requirements and should include at a minimum the protocol number, study number, subjects date of birth, BSA, dose level and calculated dose (mg), (approximate volume for infusion (mL) – if local site practice mandates this) and be signed by an Investigator. The prescription may be sent in advance to the pharmacy to assist with dose preparation, however drug should not be released until a signed prescription form has been provided. Cycle 1 Day 1 Weight should be used to calculate BSA. Standard practice for each individual site to calculate BSA dosing should be used, for example, DFCI/BWH standard of practice is to calculate BSA for dosing and to recalculate doses when there is a >10% change in weight. Please note that DuBois formula can be used per DFCI Institutional Standard.

QBS10072S drug products will be supplied as a sterile, white to off-white lyophilized powder, in single-dose glass vial in individual carton, for intravenous use. Each vial contains 50 mg QBS10072S free base and 2700 mg Betadex Sulfobutyl Ether Sodium, NF. The lyophilized powder with excipient will be reconstituted with 0.9% Sodium Chloride Injection, USP to a concentration of 50 mg/10 mL (5 mg/mL). The resulting solution will be further diluted to 0.5 mg/mL for intravenous infusion.

The study reconstitution and dilution instructions are described in the table below.

	Dose Preparation Instructions for syringe administration		*E.g. Dose Level 1, 3 mg/m², Patient Height 162cm, Weight 62kg*
Step 1.	Reconstitute QBS10072S drug product in normalsaline solution (0.9% Sodium Chloride Injection, USP) to a concentration of 50 mg/10 mL (5 mg/mL)	**Inject 8.3 mL 0.9% Sodium Chloride Injection into vial.**The normal saline (0.9% Sodium Chloride Injection, USP) used to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline.	*50 mg QBS10072S in 10 mL*
Step 2	Calculate the Volume of 0.5 mg/mL QBS10072S to be infused	**Dose Level x BSA = QBS10072S (mg) / 0.5 mg/mL (Infusion concentration) = Volume to be infused (mL)**	*3mg/m² X 1.67m² =5.01* *5.01mg/ 0.5mg/mL= 10.02mL*
Step 3	Determine primary dosing container and consumables	Where volume to be infused is **≤20mL**, drug will be administered using a **syringe pump**. A list of approved syringes and consumables can be found in Appendix 1 of the Pharmacy Manual.	*10.02mL < 20mL*
Step 4	Calculate the volume of 0.5 mg/mL solution to be prepared.	**[Volume to be infused (mL)+ priming volume*]+ 10% overage = volume of 0.5 mg/mL solution to be prepared**** *Priming volumes are listed in Appendix 1 of the Pharmacy Manual. **Round to the nearest 1mL	*[10.02mL+1.2mL + 0.7mL]*1.1 = 13.11mL* *13mL Rounded*
Step 5	Admix the 5 mg/mL QBS10072S with 0.9% Sodium Chloride UPS, in the primary container using a 1/10 dilution	Volume $_{(5\ mg/mL)}$ = Volume $_{(0.5\ mg/mL)}$ x 0.5 mg/mL / 5 mg/mL = XX.X mL Volume $_{(0.9\%\ Sodium\ Chloride\ Injection,\ UPS)}$ = Volume $_{(0.5\ mg/mL)}$ – Volume $_{(5\ mg/mL)}$	*The volume of QBS10072S solution required is 13mL, with concentration 0.5 mg/mL.* *How much 5 mg/mL QBS10072S is needed?* *Volume $_{(5mg/mL)}$ = 13ml * 0.5mg/ml / 5mg/ml =* ***1.3mL*** *How much 0.9% Sodium Chloride UPS is needed? Volume $_{(0.9\%\ Sodium\ Chloride}$ Injection, UPS) 13mL-1.3mL =* ***11.7mL***

	Dose Preparation Instructions for large volume infusion (Viaflex bag)		*E.g. Dose Level 3, 12 mg/m^2, Patient Height 162cm, Weight 62kg*
Step 1.	Reconstitute QBS10072S drug product in normalsaline solution (0.9% Sodium Chloride Injection, USP) to a concentration of 50 mg/10 mL (5 mg/mL)	**Inject 8.3 mL 0.9% Sodium Chloride Injection into vial.** The normal saline (0.9% Sodium Chloride Injection, USP) usedto reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline.	*50 mg QBS10072S in 10 mL*
Step 2	Calculate the Volume of 0.5 mg/mL QBS10072S to be infused	**Dose Level x BSA = QBS10072S (mg) / 0.5 mg/mL (Infusion concentration) = Volume to be infused (mL)**	*12mg/m^2 X 1.67m^2 =20.04* *20.04mg/ 0.5mg/mL= 40.08mL*
Step 3	Determine primary dosing container and consumables	Where volume to be infused is **>20mL**, drug will be administered using an **Infusion pump**. A list of approved IV Bags and consumables can be found in Appendix 1 of the Pharmacy Manual. ***Please note that per standard practice at DFCI, volumes < 50ml are administered via syringe pump.***	*40.08mL > 20mL*
Step 4	Calculate the volume of 0.5 mg/mL solution to be prepared.	**[Volume to be infused (mL)+ priming volume*]+ 10%overage = volume of 0.5 mg/mL solution to be prepared**** *Priming volumes are listed in Appendix 1 of the Pharmacy Manual. **Round to the nearest 1mL	*[40.08mL+ 25mL]*1.1 = 71.588mL* *72mL Rounded*
Step 5	Admix the 5 mg/mL QBS10072S with 0.9% Sodium Chloride UPS, in the primary container using a 1/10 dilution	Volume $_{(5\ mg/mL)}$ = Volume $_{(0.5\ mg/mL)}$ x 0.5 mg/mL / 5 mg/mL = XX.X mL Volume $_{(0.9\%\ Sodium\ Chloride\ Injection,\ UPS)}$ = Volume $_{(0.5\ mg/mL)}$ – Volume $_{(5\ mg/mL)}$	*The volume of QBS10072S solution required is 72mL, with concentration 0.5 mg/mL.* *How much 5 mg/mL QBS10072S is needed?* *Volume $_{(5mg/mL)}$ = 72ml * 0.5mg/ml / 5mg/ml =* ***7.2mL*** *How much 0.9% Sodium Chloride UPS is needed?* *Volume $_{(0.9\%\ Sodium\ Chloride}$ Injection, UPS) 72mL-7.2mL =* ***64.8mL***

- ***Please note: The pharmacy manual was originally written for a different trial but contains information applicable to the INSIGhT trial (DF/HCC #16-443). Refer to Appendix 11 of the pharmacy manual for DFCI specific clarifications regarding dose levels, dose calculations and IP preparation instructions.***
- ***Medfusion 3500 syringe pumps (in use at MGH) have been approved by Quadriga for use.*** *Cycle 1 Day 1 Weight should be used to calculate BSA.*

Use normal saline solution (0.9% Sodium Chloride Injection, USP) (8.3 mL as directed) to reconstitute QBS10072S and make a 50 mg/10 mL (5 mg/ mL) nominal concentration of QBS10072S. The normal saline used to reconstitute each vial should appear to be assisted or pulled into the vial by the negative pressure (partial vacuum) present in the vial. Discard any vial (and replace with another vial) if there is no vacuum present when reconstituting the vial with normal saline. The reconstituted QBS10072S drug product is stable for 24 hours at refrigerated temperature (2~8 °C) without any precipitation due to the high solubility. The reconstituted QBS10072S drug product is stable for 2 hour at room temperature.

- Calculate the required volume of QBS10072S needed for a patient's dose and withdraw that volume from the vial(s).
- Add the required volume of QBS10072S to the appropriate volume of 0.9% Sodium Chloride Injection, USP to a final concentration of 0.5 mg/mL. The QBS10072S admixture solution is stable for 4 hours at room temperature.

The combined storage time of the reconstituted solution (5mg/mL) and the admixture solution (0.5 mg/mL) for the diluted drug product must not exceed 4 hours at room temperature or 24 hours under refrigerated conditions.

7.1.8 Administration

Upon receipt of the prepared syringe or bag, QBS10072S will be administrated by an appropriately qualified and experienced member of the study staff.

QBS10072S has not been shown to be either an irritant or vesicant when administered intravenously preclinically. However, this class of medication may cause local tissue damage should extravasation occur. **Do not administer by direct injection into a peripheral vein**.

Administer QBS10072S by injecting slowly into a fast-running IV infusion or via an injection port, or via a central venous line. QBS10072S dosages should be administered concurrently with a fast-running infusion of compatible **IV fluid**.
Please note that Sodium Chloride 0.9% is the only compatible fluid to be run in conjunction with QBS10072S, and should be administered at a rate of 250mL/hr NS over 2 hours starting 1 hr before study drug

The administration of QBS10072S should be in conjunction with free flowing compatible IV solution. For participants in safety lead in cohort with PKs being drawn, the volume and administration rate of the compatible solution during the 60-minute infusion should be fixed to enable consistency of interpretation of PK data to the greatest extent possible.
Identification of the most appropriate cannulation site should be undertaken before insertion. If venous access continually proves difficult, placement of a central venous access device should be considered.

Identification of the most appropriate cannulation site should be undertaken before insertion. If venous access continually proves difficult, placement of a central venous access device should be considered.

QBS10072S should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Identification of the most appropriate cannulation site should be undertaken before insertion. If venous access continually proves difficult, placement of a central venous access device should be considered.

Premedication is recommended for all patients, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory agent (including corticosteroids), or pain reliever.

Administer the QBS10072S diluted product over a minimum of 30 minutes. First infusion should be over 60 minutes, subsequent infusion times may be decreased upon determination of patient tolerance.

Complete administration within 4 hours of QBS10072S admixture solution.

7.1.9 Ordering

The agent will be ordered from each institution's individual pharmacy (or designee) using a Quadriga Biosciences online drug ordering system. Access to this system will be requested for each institution's pharmacy by the DFCI Coordinating Center once local IRB approval is received. Anticipate 3-5 business days to receive drug after the order is placed.

7.1.10 Accountability

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

7.1.11 Destruction and Return

QBS10072S will be destroyed on site according to institutional policies, documented in the Drug Accountability Record Form. At the time of expiration / study close, a drug disposition form provided by Quadriga Biosciences will be sent out to be signed off by the Pharmacist and Investigator verifying the destruction of drug. At the end of the study, unused supplies of QBS10072S should be destroyed or returned to Quadriga Biosciences according to institutional policies. Destruction or return will be documented in the Drug Accountability Record Form.

8. STUDY CALENDAR - Initiation/Concomitant Cycle (All dose levels)

Assessment	Screen-ing[a]	Initiation/Concomitant Cycle									Adjuvant Cycles-See Adjuvant Cycles Calendar D1[f]	End of Tx[g]	30-Day Post Drug[h]	Active Follow-Up[i]	Long Term Follow-Up[j]
		D1[b]	D8[c]	D15[c]	D22[c]	D29[c]	D36[c]	D43-49[d]	D57[e,c]	D64[e,c]					
Informed Consent[k]	X														
Medical History[l]	X														
Inclusion/Exclusion Criteria[m]	X														
Vital signs[n]	X	X	X	X	X	X	X	X	X	X		X			
Physical Exam	X	X			X			X				X			
Neurologic Exam	X	X			X			X				X			
Karnofsky Performance Status(KPS)[o]	X	X			X			X				X			
Concomitant Medications[p]	----------X----------														
Adverse Events[q]		----------X----------													
Pregnancy Test (β-HCG)[r]	X	X										X			
Coagulation[s]	X														
Hematology[s]	X	X	X	X	X	X	X	X	X	X		X			
8-hour Fasting Serum Chemistry[t]	X	X	X	X	X	X	X	X	X	X		X			
HbA1c[aa]		X						X				X			
8 –hour Fasting Lipid Profile[aa]		X						X				X			
12-lead ECG[u]	X	X[u]													
Radiation[v]		----------X----------													
QBS10072S		X													
Imaging – MRI [w]	X											X		X	
Response Assessment[x]												X		X	
Post-treatment therapies[y]														X	X
Survival[z]														X	X
Archival Tumor Tissue[bb]	X														
Pharmacokinetic sampling[dd]		X													
Premedication [cc] (e.g., ondansetron and loratadine)		X													

a. All screening procedures to be performed within 28 days of initial registration unless otherwise specified. **NOTE: refer to section 10 of master protocol for comprehensive details on screening assessments, initial registration, randomization assignment and second registration timing.**
b. Concomitant radiation and QBS10072S must begin no later than 42 days following initial surgery. Day 1 assessments must be performed within 3 days of starting study

treatment. Screening assessments may be utilized as baseline/Day 1 assessments if they fall within window.

c. +/- 2 day window for weekly assessments during concomitant phase.
d. Day 43-49 visit to occur within +/- 7 days of completing radiation.
e. Assessment required for Safety Lead-In patients only. These assessments are able to be done locally.
f. Adjuvant C1D1 to begin ≥ 28 (+14) days following end of radiation. Cycle 1, Day 1 adjuvant assessments to be performed within 4 days of Day 1 QBS10072S. All adjuvant cycle 1, day 1 assessments must be resulted and reviewed prior to initiating treatment with QBS10072S. Day 1 assessments for subsequent adjuvant cycles to be performed within 4 day of Day 1 QBS10072S
g. End of Treatment: For participants who discontinue study treatment assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment.
h. 30-Day Post Drug: For participants who discontinue study treatment a contact/visit is to be performed 30 days (+7 days) after date of last drug taken on study. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last drug.
i. Active Follow-Up: for participants who discontinue study treatment for reasons other than disease progression, study team must continue monitoring participant's disease status by radiologic imaging at 8-week intervals (+/- 1 week) until (1) documented disease progression, (2), death, (3) participant withdraws from follow-up, or (4) end of study, whichever occurs first.
j. Long Term Follow-Up: participants will be followed every 8 weeks (+/-1 week) via contact or medical record review until death. Participants must be followed for survival data at every long-term follow-up time point and for post-treatment therapies and reason for stopping those therapies when available.
k. Informed Consent: must be obtained by MD attending. No study specific screening procedures may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration. Following initial registration and receipt of INSIGhT randomization assignment, participants must sign the consent form specific to the assigned treatment arm prior to initiating treatment for that study arm.
l. Medical History: to include review of treatment history for GBM, any ongoing medical conditions and medical history pertaining to eligibility on study and involvement during study.
m. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements for initial registration. See section 2 of this appendix for arm specific eligibility criteria.
n. Vital signs must be performed prior to administration of treatment on treatment-days. Height required only at screening. Vital Signs: Includes temperature, sitting or semi recumbent (same position must be used throughout the study and documented in source notes) blood pressure (BP), and pulse rate (to be recorded in the sitting position after 5 minutes of rest) weight, respiration rate, temperature. On Day 1 of each cycle, vital signs should be measured prior to dosing (pre dose), BP, and pulse rate will be repeated 1 hour after dosing.
o. Karnofsky Performance Status (KPS): see appendix A of master protocol.
p. Concomitant Medications: concomitant medications and reason for administration should be documented in the case history from date of consent up to the 30-Day Post Drug Visit.
q. Adverse Events: adverse events experienced by participants will be collected and recorded from the first dose of treatment on-study up to the 30-Day Post Drug Visit of the last dose of study medication (+ 7 days depending on when 30-Day Post Drug visit/contact occurs).
r. Pregnancy Test: required for women of child-bearing potential (see section 3 of master protocol for definition of women of child-bearing potential). Pregnancy test can be either blood or urine sample.
s. Coagulation: PT/INR, PT, PTT required at screening only. Hematology: erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
t. 8-hour Fasting Serum Chemistry: albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed), amylase, lipase, and magnesium.
u. For Patients in Safety Run-In and Expanded Safety Run-In cohorts: Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed

approximately 2 minutes apart (+/- 3 minutes) to determine mean QTcF interval. (See Table 2: **Electrocardiogram, Pharmacokinetic, and Biomarker Sampling Schedule).** Following safety lead-in and Expanded Safety Lead-in, EKG will be done at Screening and Initiation/Concomitant Cycle 1 Day 1 (if screening EKG is done within 7 days of Day 1, then EKG at Concomitant C1D1 is not required).

v. Radiation: see section 3.1 of this sub-study appendix for definition of standard radiation therapy per protocol.

w. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site, Appendix D Recommended MRI Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial. Local reading (investigator assessment) will be used to determine eligibility and for participant management.

x. Response Assessment: Per RANO criteria (see section 11 of master protocol).

y. Post-treatment Therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected when available.

z. Survival: date of death and reason must be collected for overall survival purposes.

aa. HbA1c & 8-hour fasting lipid profile: do not need to be resulted and reviewed prior to initiating QBS10072S with RT in the concomitant phase.

bb. Archival tumor tissue may be sent to Stanford University for assay laboratory tests.

cc. Premedication is recommended for all patients, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory (including corticosteroids), or pain reliever (see Section 7.1.8).

dd. Pharmacokinetic (PK) sampling: will be performed for patients in the safety run-in and expanded safety run-in cohorts only. See Table 2: **Electrocardiogram, Pharmacokinetic, and Biomarker Sampling Schedule**.

Adjuvant Cycles	Treatment Cycle 1				Treatment Cycle 2				Treatment Cycle 3 and beyond	

Adjuvant Cycles – 28-Day Dosing Regimen

Study Day	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15
Visit Window	28-42 days after RT completion	±2	±2	±2	±2	±2	±2	±2	±2	±2
General Assessments										
Height	X									
Weight	X				X				X	
Physical Exam	X				X				X	
Neurologic Exam	X				X				X	
Adverse Events[1]	----------X----------									
Symptom directed physical exam[2]	----------X----------									
Vital Signs[3]	X				X				X	
Triplicate ECG [4]	X				X					
KPS [5]	X				X				X	
Prior and Concomitant Medications and Procedures (e.g., surgeries)	X				X				X	
Corticosteroid utilization[6]	X				X				X	
Contraception check[8]	X				X				X	
Laboratory Assessments – Local										
Hematology[9]	X	X	X	X	X	X	X	X	X	X
Blood Chemistry[10]	X	X	X	X	X	X	X	X	X	X
Urinalysis	X				X					
Urine or Serum Pregnancy Test[7]	X				X				X	
Laboratory Assessments – Central										
Pharmacokinetic sampling[4]	X									
QBS10072S Treatment (Q4W)										
Premedication [11] (e.g., ondansetron and dexamethasone)	X				X				X	
QBS10072S Infusion [12]	X				X				X	
Efficacy Measurements										
MRI and Clinical Response Assessment (RANO)[13]	X								X	

Adjuvant Cycles – 21-Day Dosing Regimen

Adjuvant Cycles	Treatment Cycle 1			Treatment Cycle 2			Treatment Cycle 3 and beyond	
Study Day	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 15
Visit Window	28-42 days after RT completion	±2	±2	±2	±2	±2	±2	±2
General Assessments								
Height	X							
Weight	X			X			X	
Physical Exam	X			X			X	
Neurologic Exam	X			X			X	
Adverse Events[1]	----------X----------							
Symptom directed physical exam[2]	----------X----------							
Vital Signs[3]	X			X			X	
Triplicate ECG [4]	X			X				
KPS PS[5]	X			X			X	
Prior and Concomitant Medications and Procedures (e.g., surgeries)	X			X			X	
Corticosteroid utilization[6]	X			X			X	
Contraception Check[8]								
Laboratory Assessments Local								
Hematology[9]	X	X	X	X	X	X	X	X
Blood Chemistry[10]	X	X	X	X	X	X	X	X
Urinalysis	X			X				
Urine or Serum Pregnancy Test[7]	X			X			X	
Laboratory assessments Central								
Pharmacokinetic sampling[4]	X							
QBS10072S Treatment (Q3W)								
Premedication [11] (e.g., ondansetron and dexamethasone)	X			X			X	
QBS10072S Infusion [12]	X			X			X	
Efficacy Measurements [13]								
MRI and Clinical Response Assessment (RANO)	X	----------X----------						

Abbreviations: → = ongoing/continuous event; AE = Adverse event; ECG = electrocardiogram; EOS = End of study; EOT = End of treatment; MRI = Magnetic resonance imaging; PK = Pharmacokinetic; KPS = Karnofsky performance status; RANO = Response assessment in neuro-oncology; SAE = Serious adverse event.

1. *Adverse Events*: Adverse events experienced by participants will be collected and recorded from the date of first dose of treatment on-study until 30 days (+/- 7 days) after the date of the last dose of study medication. Participants who experience serious or reportable adverse events during treatment or starting within 30 days of last dose of study medication will be followed until resolution or stabilization of the event(s).
2. *Symptom directed PE:* should be performed as appropriate at other timepoints where complete physical examinations are not required.

3. *Vital Signs*: Includes temperature, sitting or semi-recumbent (same position must be used throughout the study and documented in source notes) blood pressure (BP), and pulse rate (to be recorded in the sitting position after 5 minutes of rest). On Day 1 of each cycle, vital signs should be measured prior to dosing (pre-dose). BP and pulse rate will be repeated 1 hour after the end of infusion (+/- 5 min).
4. *For Patients in Safety Run-In and Expanded Safety Run-in Cohorts only*: See Table 3: Pharmacokinetic Sampling Schedule – Adjuvant Cycle 1 for adjuvant C1D1 **ECG and PK** timepoints.
5. *KPS:* see Appendix A in master protocol
6. *Corticosteroid Utilization*: Participants' steroid dose will be recorded at each visit.
7. *Urine or Serum Pregnancy Test:* Pregnancy test for female patients of childbearing potential. Test may also be repeated as per request of Institutional Review Board/Independent Ethics Committee (IRB/IECs), if required by local regulations.
8. *Contraception Check:* The patient will be informed of the need to use highly effective contraception consistently and correctly. The conversation and patient's affirmation will be documented in the patient's chart.
9. *Hematology:* erythrocytes (RBC), hemoglobin, hematocrit, platelets, total WBC plus differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
10. *Serum Chemistry:* albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed).
11. *Premedication* is recommended for all patients, consistent with institutional guidelines, and may include an antihistamine, anti-inflammatory (including corticosteroids), or pain reliever (see Section 7.1.8).
12. Cycle 1, Day 1 adjuvant assessments to be performed within 4 days of Day 1 QBS10072S. All adjuvant cycle 1, day 1 assessments must be resulted and reviewed prior to initiating treatment with QBS10072S. Day 1 assessments for subsequent adjuvant cycles to be performed within 4 days of Day 1 QBS10072S. *QBS10072S Infusion*: Initially QBS10072S will be administered intravenously over 1 hour on day 1 of the first adjuvant cycle. After the first dose, the infusion may be decreased to a minimum of 30 minutes at the discretion of the Investigator (N.B., another dosing regimen may be later considered in the study if supported by emerging clinical data). Treatment will continue until progressive disease, unacceptable toxicity or patient refusal, whichever occurs first. If progressive disease occurs during treatment, continuation of study drug may continue, under the following conditions: (a) presence of reasonable evidence of clinical benefit; (b) absence of any relevant toxicity; and (c) after discussion with the Sponsor.
13. Efficacy Measurements: Tumor assessments will include all known or suspected disease sites brain MRI scans are to be performed every 8 weeks. The allowable time window for disease assessments is ±7 days. Tumor assessment should be repeated at the end of treatment visit if more than 4 weeks have passed since the last evaluation. When the study treatment is discontinued for reasons other than disease progression, patients should continue to have tumor assessments performed every 8 weeks (+/- 7 days) until (a) disease progression or death, (b) patient refusal or withdrawal of consent, or (c) start of another anticancer treatment, whichever occurs first. Tumor assessments should be fixed according to the calendar, regardless of treatment delays. Please see RANO Criteria for Time Point Responses in the Master Protocol.

Table 2: Safety Lead-In and Expanded Safety Lead-In Electrocardiogram and Pharmacokinetic Sampling Schedule – Concomitant/Initiation Cycle (QBS10072S + Radiation Therapy)

	Concomitant Cycle 1												Unscheduled (as needed)[4]
Study Day	Day 1											Day 2	
	Predose[2]	Post start of infusion		End of infusion	Post end of infusion[4]								
Time Post-dose[1]		15 m	30 m		5 m	30 m	1 h	2 h	3 h	5 h	7 h	24 h	
Window		±5 m	±5 m	PK within 2m prior to EOI ECG within 6m prior to EOI	+10 m	±5 m	±5 m	±5 m	±10 m	±10 m	±20 m	±1 h	
Plasma for QBS10072S PK[2]	X	X	X	X	X	X	X	X	X	X	X	X	
Triplicate ECGs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ECG = Electrocardiogram; EOI = End of Infusion; h = hour; m = minute; PK = Pharmacokinetics.

1. Collection Time: Sampling times are related to morning dose; this schedule assumes a 60-minute infusion period, adjustments will be made according to infusion time
2. Pharmacokinetics: Blood samples for determination of plasma QBS10072S drug concentrations will be collected at the time points specified **only on patients in the safety run-in cohort** (NOTE: PK sampling time points may change [e.g., duration of infusion] pending PK data from early dose levels, but the total number of samples will remain the same).
3. For Safety Run-In cohort: Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart (+/- 3 minutes) to determine mean QTcF interval. All ECG collection time points are with respect to QBS10072S dosing. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation.
4. Additional samples may be collected at the discretion of the Investigator (e.g., adverse events).

Table 3: Safety Lead-In and Expanded Safety Lead-In Pharmacokinetic Sampling Schedule – Adjuvant Cycle 1

Study Day	Adjuvant Cycle 1 Day 1								
	Predose[2]	Post start of infusion		End of infusion	Post end of infusion[4]				
Time Postdose[1]		15 m	30 m		5 m	30 m	1 h	2 h	3 h
Window		±5 m	±5 m	PK within 2 m prior to EOI ECG within 6m prior to EOI	+10 m	±5 m	±5 m	±5 m	±10 m
Plasma for QBS10072S PK[2]	X	X	X	X	X	X	X	X	X
Triplicate ECGs[3]	X	X	X	X	X	X	X	X	X

Abbreviations: ECG = Electrocardiogram; EOI = End of Infusion; h = hour; m = minute; PK = Pharmacokinetics.

1. Collection Time: Sampling times are related to morning dose; this schedule assumes a 60-minute infusion period, adjustments will be made according to infusion time
2. Pharmacokinetics: Blood samples for determination of plasma QBS10072S drug concentrations will be collected at the time points specified **only on patients in the safety run-in cohort** (NOTE: PK sampling time points may change [e.g., duration of infusion] pending PK data from early dose levels, but the total number of samples will remain the same).
3. Triplicate 12 lead ECG: At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart (+/- 3 minutes) to determine mean QTcF interval. Starting at Cycle 3, ECGs can be performed as clinically indicated. All ECG collection time points are with respect to QBS10072S dosing. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If the mean QTcF is prolonged (value of >480 msec), the ECGs should be reevaluated by a qualified person at the institution for confirmation.
4. Additional samples may be collected at the discretion of the Investigator (e.g., adverse events).

9. Measurement of Effect

Refer to section 11 of master INSIGhT protocol for details on measurement of effect.

10. REFERENCES

1. Bessho, T. *Induction of DNA Replication-mediated Double Strand Breaks by Psoralen* DNA Interstrand Cross-links J. Bio Chem 2003 *278*: 5250-5254
2. Colvin M. Alkylating Agents. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. *Holland-Frei Cancer Medicine*. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK12772/

3. Preuss I, Thust R, Kaina B. *Protective effect of O6-methylguanine-DNA methyltransferase (MGMT) on the cytotoxic and recombinogenic activity of different antineoplastic drugs*. Int J Cancer. 1996;65(4):506- 12.

4. Duelli R, Enerson BE, Gerhart DZ, Drewes LR. *Expression of large amino acid transporter LAT1 in rat brain endothelium*. J Cereb Blood Flow Metab. 2000;20(11):1557-62.

5. Matsuo H, Tsukada S, Nakata T, Chairoungdua A, Kim DK, Cha SH, et al. *Expression of a system L neutral amino acid transporter at the blood-brain barrier*. Neuroreport. 2000;11(16):3507-11.

6. Killian DM, Chikhale PJ. *Predominant functional activity of the large, neutral amino acid transporter (LAT1) isoform at the cerebrovasculature*. Neurosci Lett. 2001;306(1-2):1-4.

7. Nawashiro H, Otani N, Shinomiya N, Fukui S, Ooigawa H, Shima K, et al. *L-type amino acid transporter 1 as a potential molecular target in human astrocytic tumors*. Int J Cancer. 2006;119(3):484-92.

8. Sakata T, Ferdous G, Tsuruta T, Satoh T, Baba S, Muto T, et al. *L-type amino-acid transporter 1 as a novel biomarker for high-grade malignancy in prostate cancer*. Pathol Int. 2009;59(1):7-18.

9. Ichinoe M, Mikami T, Yoshida T, Igawa I, Tsuruta T, Nakada N, et al. *High expression of L-type amino- acid transporter 1 (LAT1) in gastric carcinomas: Comparison with non-cancerous lesions*. Pathol Int. 2011;61(5):281-9.

10. Haining Z, Kawai N, Miyake K, Okada M, Okubo S, Zhang X *Relation of LAT1/4F2hc expression with pathological grade, proliferation and angiogenesis in human gliomas*. BMC Clin Pathol. 2012;12:4.

11. Isoda A, Kaira K, Iwashina M, Oriuchi N, Tominaga H, Nagamori S, et al. *Expression of L-type amino acid transporter 1 (LAT1) as a prognostic and therapeutic indicator in multiple myeloma*. Cancer Sci. 2014;105(11):1496-502.

12. Youland RS, Kitange GJ, Peterson TE, Pafundi DH, Ramiscal JA, Pokorny JL, et al. *The role of LAT1 in18F-DOPA uptake in malignant gliomas. Journal of neuro-oncology*. 2013;111(1):11-8.

DFCI REPORTABLE AE COVERSHEET – INSIGHT QBS10072S ARM

DF/HCC Protocol No. 16-443 **Quadriga Biosciences Tracking No.** QBS10072S -

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this AE):

☐ Dr. Patrick Y. Wen and Dana-Farber Coordinating Center
Email: NeuroOnc_SAE@dfci.harvard.edu

☐ Quadriga Biosciences Corporation
Email: ron.weitzman@quadrigabiosciences.com
Email: Trinh Le trinh@ccrc-inc.com

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

Participant # and Initials:
Date Event Met Reporting Criteria (as defined in protocol):
Type of Report: ☐Initial ☐Follow-up

CTCAE Event #1 Description:	CTCAE Event #2 Description (if applicable): *NOTE: use another coversheet if more than 2 events are being reported at this time*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death
Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness to **QBS10072S**: ☐Expected ☐Unexpected ☐ N/A	Expectedness to **QBS10072S**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **QBS10072S**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **QBS10072S**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Reporting Investigator (print):	

Signature of Reporting Investigator: _____ Date: _____

APPENDIX J Study Drug VBI-1901/BALSTILIMAB ARM OF INSIGhT

TABLE OF CONTENTS

Contents

1. BACKGROUND

1.1 Study Drug VBI-1901

Virus-Like Particles to Design New Vaccines

Natural viruses are made of proteins associated with either DNA or RNA. They need to infect cells (e.g., human or animal cells) in order to hijack the cellular machinery and produce new viruses using the viral DNA and RNA component as a template. Moreover, some viruses, also called enveloped viruses, are released by budding through the infected cell membrane, therefore being enveloped in a fragment of the lipid bilayer from the host cell membrane.

Under certain conditions, virus-like particles (VLPs), very similar to the parental virus but devoid of the viral DNA or RNA, can be produced[1]. Moreover, VLPs can be engineered to carry heterologous antigens against other infectious diseases. VLPs are highly immunogenic leading to the development of several "third generation" prophylactic vaccines. For instance, VLPs are regarded as safe and efficient prophylactic vaccines against infectious diseases including human papillomavirus and hepatitis B[2].

Enveloped virus-like particles (eVLPs) are an innovative new class of synthetic vaccines that are designed to closely mimic the structure of enveloped viruses and are comprised of a lipid bilayer and a protein core essentially of viral origin (see Figure 1 below). It is possible to design eVLPs carrying several antigens and for instance able to activate both the cellular and humoral immune responses.

Rationale for Selecting the Components of VBI-1901

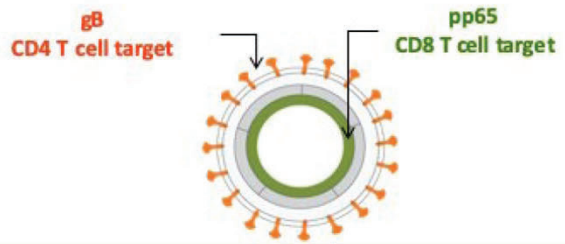
VBI Vaccines Inc. (VBI) designed an eVLP based on a well-known retrovirus, the Moloney Leukemia virus that has been widely used in gene therapy, carrying two human cytomegalovirus (HCMV) antigens, glycoprotein B (gB) and 65-kiloDalton polypeptide (pp65). A summary of the design and rationale for the vaccine candidate VBI-1901 appears in Figure 1.

MLV Gag Component

Moloney Leukemia virus (MoMLV or MLV) belongs to the family of Retroviridae, Gammaretroviral Genus and has been widely used in gene therapy, including in clinical trials. All retroviruses express the group of antigens (Gag) protein although each Gag may be slightly different depending on the species and host. VBI's eVLP platform technology uses MLV Gag polypeptides as the basis of VLP formation. In the retrovirus, Gag protein yields the viral matrix (MA), capsid (CA), and nucleocapsid (NC) proteins after being cleaved by viral and/or cellular proteases[3-5]. The capsid protein is the main structural element of mature virus particles, forming the core shell around the NC-RNA complex, while the MA remains linked to the viral lipid bilayer (envelope). Native viral Gag polypeptides inherently include in their C-terminal the Pol protein (containing protease, reverse transcriptase, and integrase functions). However, VLP formation does not require the presence of these components and VBI's eVLP technology does not include the Pol polyprotein. Gag alone can assemble into VLPs[6] and fusion of small proteins such as green

fluorescent protein to Gag does not alter this property[7]. To ensure expression of the HCMV tegument protein pp65 into the eVLP, pp65 is directly fused to the MLV Gag.

Figure 1: Design of GBM HCMV eVLP Vaccine Candidate VBI-1901



Vaccine Component	Immune Response	Scientific Support
CMV gB	Antibody response against gB expressed on surface of tumor cells Polyvalent CD4+ T helper response	• Prevent gB activation of PDGFR-AKT signaling in tumor cells (*Cobbs C, 2014*) • Antibody-dependent cell cytotoxicity (ADCC)-mediated tumor cell destruction/immune activation
CMV pp65	Polyvalent CD4+ T helper cell & CD8+ CTL responses	• CMV pp65 vaccination with dendritic cell activation prolongs survival of GBM patients (*Mitchell DA, 2015*) • Responses against multiple epitopes and antigens (gB & pp65) avoid immunoselection/tumor escape
eVLP formulation with GM-CSF	GM-CSF augments tumor-specific IFN-γ and CCL3 responses	• Clinical data demonstrate IFN-γ and CCL3 as key biomarkers of efficacious tumor immunity (*Galon J et al, 2006; Mitchell DA et al, 2015*)

CMV = cytomegalovirus; eVLP = enveloped virus-like particle; gB = glycoprotein B; GBM = glioblastoma; GM-CSF = granulocyte-macrophage colony-stimulating factor; HCMV = human cytomegalovirus; IFN-γ = interferon-γ; pp65 = 65-kiloDalton polypeptide
Note: See references 8-10.

HCMV pp65 Component

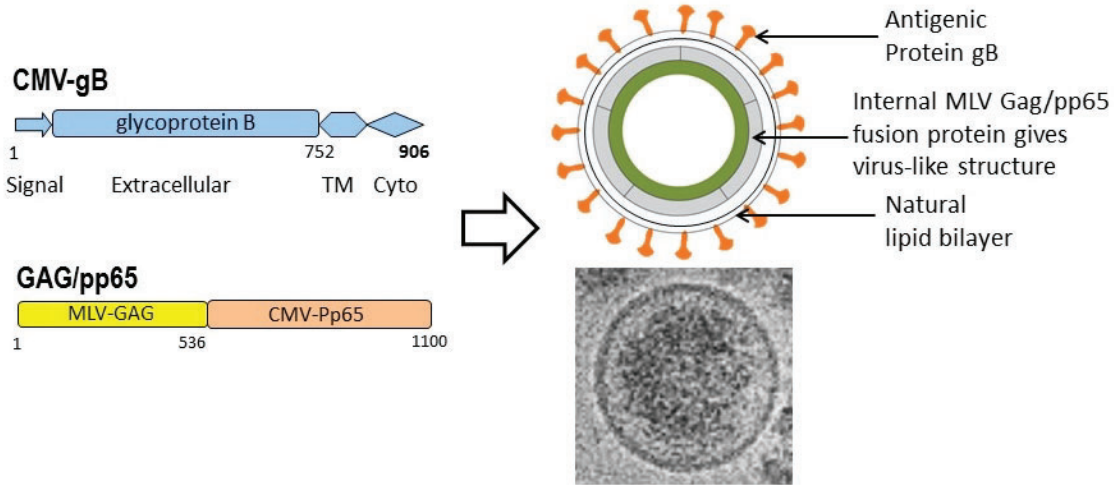
Located within the tegument between the capsid and the viral envelope, HCMV pp65 is the major constituent of extracellular virus particle antigens. Antigen pp65 is a component specific to the therapeutic vaccine developed by VBI and is a major target of the cytotoxic T-cell response[11]. It is thought to play a major role in the immune evasion during HCMV infections by preventing infected cells from being destroyed by the immune system[11].

HCMV gB Component

Glycoprotein B is one of the major B-cell antigens in HCMV, inducing neutralizing, protective immune responses and used as a target in several vaccine trials[12]. VBI has demonstrated that eVLPs expressing HCMV gB induce potent humoral immune responses in mice and rabbits[13]. In VBI-1901, eVLPs are produced after transient transfection of HEK 293 cells with plasmid encoding murine leukemia virus Gag plasmid fused in-frame with HCMV pp65 antigen, which gives rise to particles. Co-transfected HCMV gB plasmid enables particles budding from the cell surface to incorporate the gB protein into the lipid bilayer.

The design schematic of VBI-1901 is presented in Figure 2.

Figure 2: Design Schematic and Electron Microscopy Image of VBI-1901



CMV = cytomegalovirus; GAG = group of antigens; gB = glycoprotein B; MLV = murine leukemia virus; pp65 = 65-kiloDalton polypeptide

GM-CSF as Adjuvant

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is used for the mobilization of hematopoietic progenitor cells after chemotherapy or before hematopoietic cell collection for transplantation[14]. Since initial studies demonstrating that vaccination with irradiated tumor cells genetically modified to produce GM-CSF promoted potent anti-tumor immunity[15], an expanding role for GM-CSF in regulating immune responses has been recognized based upon its activity on the development and maturation of antigen presenting cells and its capability for skewing the immune system toward Th1-type responses[16]. As a consequence, GM-CSF has been proposed as an adjuvant in cancer immunotherapy[17] including for the treatment of glioblastoma[18].

Supporting Clinical Data

Safety data from 18 subjects who received VBI-1901 plus GM-CSF as Part A of the study demonstrated that the vaccine was well tolerated with no safety signals identified. The majority of adverse experiences associated with vaccinations were transient mild to moderate injection site reactions.

Table 1 lists the nine serious adverse events (SAEs) that occurred in six subjects during Part A of the study. All the SAEs were assessed by study investigators as either not related (n=4) or unlikely related (n=5) to the study vaccine.

Table 1: Serious Adverse Events Observed with VBI-1901 plus GM-CSF

Subject ID	AE Preferred Term [a]	AE Severity [b]	AE Causality [b]
01-003	Urinary tract infection	Grade 3	Not related
01-004	Metapneumovirus infection	Grade 1	Not related
01-004	Glioblastoma multiforme	Grade 4	Not related
01-018	Gait disturbance	Grade 3	Not related
03-001	Wound infection	Grade 3	Unlikely related
03-001	Embolism	Grade 4	Unlikely related
03-004	Seizure	Grade 1	Unlikely related
03-004	Seizure	Grade 1	Unlikely related
03-006	Colloid brain cyst	Grade 1	Unlikely related

[a] MedDRA v21.0
[b] Investigator's assessment

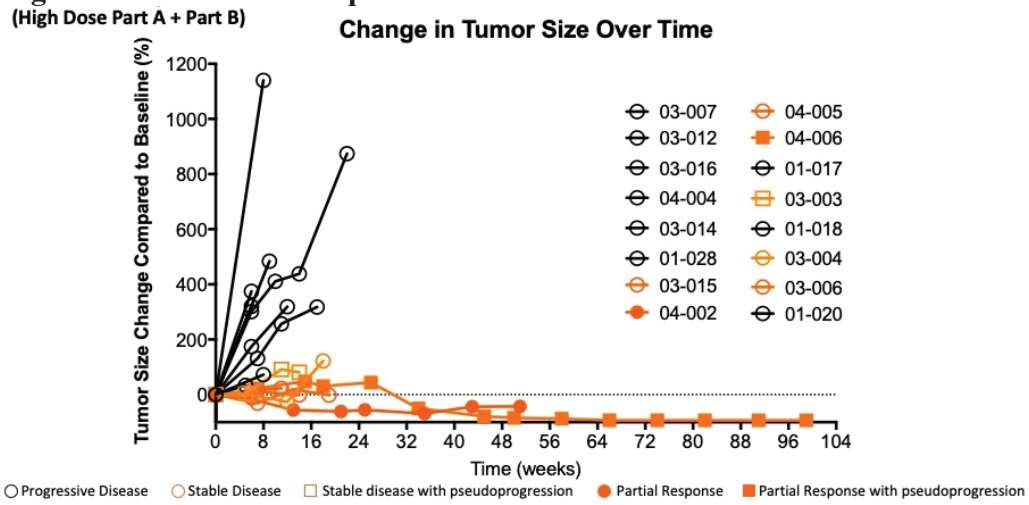
There were no on-study deaths reported during the Part A of the study. Three subjects with advanced GBM died following discontinuation from the study. The first subject (03-001), a 54-year-old white female with advanced GBM who completed 2 cycles of VBI-1901 vaccination at the intermediate dose (2 µg pp65), developed a thromboembolic event and decided to discontinue from the study to pursue palliative care. This subject later died off-study - the cause of death was not reported. The second subject (01-003), a 54-year-old white female with advanced GBM, completed 8 cycles of VBI-1901 vaccination at the low dose (0.4 µg pp65) before discontinuing from the study. This subject later died off-study - the cause of death was not reported. The third subject (01-009), a 57-year-old white male with advanced GBM, completed 2 cycles of VBI-1901 vaccination at the low dose (0.4 µg pp65) before discontinuing from the study. This subject later died off-study - the cause of death was not reported.

On December 19, 2018, the data and safety monitoring board (DSMB) reviewed the safety information for all the subjects that were enrolled in the high dose cohort. No concerns were identified, and the DSMB, in agreement with the sponsor and the medical monitor, unanimously recommended moving forward with the next phase of the study (Part B).

Immunogenicity data have demonstrated that the vaccine boosts CMV-specific T cell and antibody responses in a subset of subjects across all dose levels. Tumor responses (stable disease) were observed in 3/6 subjects in the high dose cohort but in only 1/12 subjects in the low and intermediate dose cohorts, prompting the sponsor to select the high (10 µg pp65) dose of VBI-1901 in the Part B extension phase of the study.

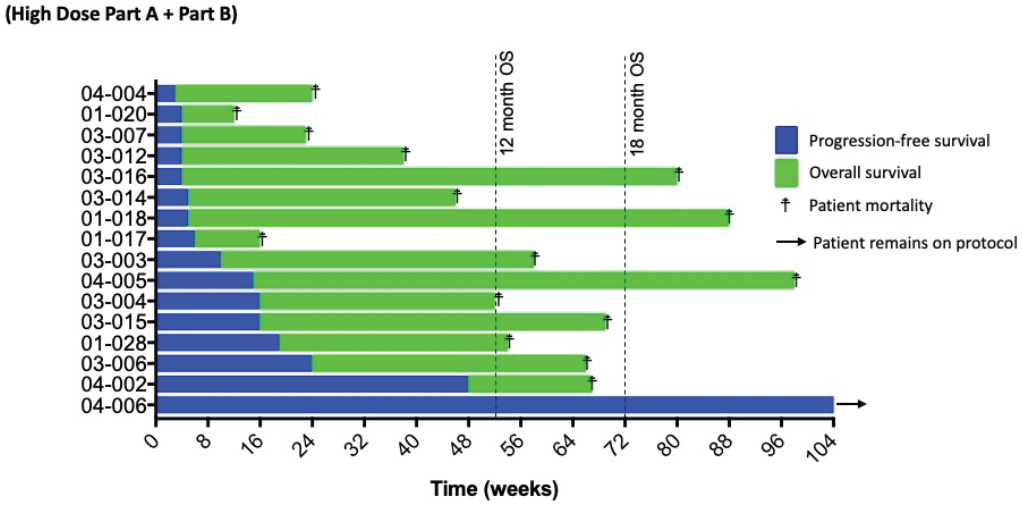
Four among 10 subjects treated in the Part B extension phase of the study with VBI-1901 plus GM-CSF had tumor responses: 2 stable disease, 2 partial responses. A disease control rate (SD+PR+CR) of 44% was observed when combining all patients that received the same high dose level of VBI-1901 plus GM-CSF (Figure 3). No vaccine-related SAEs have been reported in Part B of the study.

Figure 3: Tumor Responses Associated with VBI-1901+GM-CSF Treatment



A 12 month OS rate of 62.5% and mOS of 13 months seen with the high 10µg pp65 dose of VBI-1901 plus GM-CSF treatment compares favorably to historical standard of care treatments (Taal, 2014).

Figure 4: Clinical Responses Associated with VBI-1901+GM-CSF Treatment



Balstilimab (AGEN2034)

Balstilimab (AGEN2034) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody designed to antagonize inhibitory signaling in a manner comparable to nivolumab by the programmed cell death protein 1 (PD-1) pathway via blockade of PD-1 binding to programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2).

Supporting Nonclinical Data

The utility of PD-1 as a therapeutic antibody target in human cancer has been well characterized. A human IgG4 antibody with Ig kappa light chains (IgG4κ) monoclonal antibody (mAb) directed against PD-1 (nivolumab, Opdivo®) has been evaluated in thousands of patients comprising a range of intravenous (IV) doses, from 0.1 mg/kg to 20 mg/kg[19]. Balstilimab is physicochemically comparable to nivolumab (anti-PD-1 specific IgG4 antibodies with Igκ light

chains), and a side-by-side in vitro pharmacological characterization of balstilimab and nivolumab demonstrated that these two antibodies were functionally comparable.

Balstilimab toxicity was assessed in a 4-week Good Laboratory Practice (GLP) repeat dose study in cynomolgus monkeys and in a human tissue cross reactivity study. No clinically relevant findings were identified.

Details of these studies can be found in the Balstilimab Investigator's Brochure.
The no-observed-adverse-effect level (NOAEL) of balstilimab from the 4-week cynomolgus monkey toxicity study was 40 mg/kg. Histopathology findings at 300 mg/kg included vascular/perivascular inflammation in a variety of tissues. The collective histology, immunohistochemistry, pharmacokinetics (PK) and anti-drug antibody (ADA) data were consistent with an immune-mediated vasculitis caused by ADA formation in a proportion of monkeys given 300 mg/kg balstilimab. ADA is a recognized phenomenon in non-human primate studies as it relates to the antigenicity of an administered humanized antibody and these types of events are typically not correlated with the formation of ADA in human patients[20-22]. Other treatment-related findings in the 4-week study were consistent with pharmacodynamic effects including changes in lymphoid cellularity in the spleen (increased at ≥ 40 mg/kg) and thymus (decreased at 300 mg/kg) and an increase in mononuclear cell infiltration in the brain (≥ 40 mg/kg). These findings related to some changes in organ weights that showed a trend towards recovery following the 4-week non-dosing phase. Cytokine measurements from the 4-week toxicity study in cynomolgus monkeys and from an in vitro cytokine release assay in human whole blood revealed no findings that are considered related to cytokine release syndrome.

For detailed information on preclinical characterization, manufacturing, and administration of balstilimab, please refer to the Balstilimab Investigator's Brochure.

Supporting Clinical Data

Currently, the balstilimab clinical program consists of multiple ongoing clinical studies, including C-700-01, C-550-01, C-750-01/GOG-3028, C-800-01, and C-1100-01, in patients with metastatic or locally advanced solid tumors (advanced tumors) (C-800-01 and C-1100-01) and with expansion into selected solid tumors (cervical cancer) (C-700-01 and C-550-01) or in advanced cervical cancer (C-750-01/GOG-3028). Balstilimab is being evaluated both as a single agent and in combination with either zalifrelimab, AGEN1181, or AGEN2373.

Study C-700-01 is an ongoing Phase 1/2, open-label clinical study of balstilimab as a single agent. Phase 1 is a dose escalation study in patients with metastatic or locally advanced solid tumor for which no standard therapy exists or standard therapy has failed. Phase 2 expansion evaluates the efficacy, safety, and PK in patients with locally advanced, recurrent, and/or metastatic cervical cancer and who have relapsed after platinum-based chemotherapy.

Study C-550-01 is an ongoing Phase 1/2 open-label clinical study of zalifrelimab (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] antagonist) in combination with balstilimab. Phase 1 is a dose escalation study in patients with metastatic or locally advanced, solid tumor for which no standard therapy exists or standard therapy has failed. Phase 2 expansion evaluates the

efficacy, safety, and PK in patients with locally advanced, recurrent, and/or metastatic cervical cancer and who have relapsed after a platinum-based chemotherapy (first-line).

Study C-750-01/GOG-3028 is an ongoing Phase 2, randomized, blinded, noncomparative clinical study evaluating the efficacy and safety of balstilimab as monotherapy administered with placebo (Treatment Arm 1) or in combination with zalifrelimab (Treatment Arm 2) in women with metastatic, locally advanced, and/or recurrent cervical cancer (second line) - RaPiDs.

Study C-800-01 is an ongoing Phase 1/2 trial evaluating AGEN1181 (fragment crystallizable [Fc]-engineered CTLA-4 antagonist) as a monotherapy and in combination with balstilimab in patients with advanced and/or refractory malignancies.

Study C-1100-01 is an ongoing, Phase 1, open-label, multicenter clinical study using a 3+3 design in patients with a histologically or cytologically confirmed diagnoses of metastatic or locally advanced solid tumor for which no standard therapy is available or standard therapy has failed. AGEN2373 will be evaluated in 3 treatment arms, AGEN2373 as monotherapy administered every 2 weeks (Q2W), as monotherapy administered every 4 weeks, or as combination therapy with balstilimab administered Q2W to assess the safety, tolerability, and dose-limiting toxicity (DLT) of AGEN2373.

Across the studies, the most frequently reported treatment-emergent adverse events (TEAEs) (≥ 10%) by preferred term (PT) regardless of relationship to study drug were anaemia (36.4%), nausea (29.5%), fatigue (26.5%), diarrhoea (25.4%), vomiting (22.0%), constipation (18.5%), urinary tract infection (18.5%), abdominal pain (18.1%), pyrexia (17.5%), asthenia (17.2%), decreased appetite (16.6%), back pain (15.1%), cough (13.4%), headache (12.3%), pruritus (11.4%), hypothyroidism (10.6%), blood creatinine increased (10.3%), and arthralgia (10.1%). The most frequently reported treatment-related TEAEs (≥ 10%) were fatigue (16.4%), diarrhoea (14.0%), and nausea (11.6%). Seven (1.5%) patients experienced Grade 4 treatment-related TEAEs including lipase increased, adrenal insufficiency, anaemia, lymphopenia, and uncoded (1 patient each), and hypokalaemia (2 patients). Most treatment-related TEAEs were of mild or moderate intensity.

Across the studies, 208 patients experienced at least 1 serious adverse event (SAE). The most frequently reported SAEs by PT regardless of relationship occurring in ≥ 5 patients included acute kidney injury, general physical health deterioration, tumour pain, urinary tract infection, abdominal pain, pneumonia, immune-mediated enterocolitis, intestinal obstruction, renal failure, anaemia, cancer pain, pneumonitis, tumor hemorrhage, back pain, diarrhoa, pyrexia, vomiting, and sepsis. A total of 52 patients experienced at least 1 treatment-related SAE. Treatment-related SAEs that occurred in ≥ 3 patients by PT included immune-mediated enterocolitis (8 patients), diarrhoea (5 patients), pneumonitis (5 patients), vomiting (4 patients), colitis (3 patients), and immune-mediated nephritis (3 patients).

A total of 182 deaths were reported across the studies as of 20 December 2020. Grade 5 treatment-related adverse events (AEs) occurred in 5 patients and included hepatitis, death, pneumonitis, immune-mediated nephritis, and sepsis.

Data from 464 patients enrolled in the C-700-01, C-550-01, C-750-01/GOG-3028, and C-800-01

studies are presented through a data cutoff date of 21 December 2020. Overall, balstilimab has been well tolerated. Balstilimab monotherapy or in combination with zalifrelimab or AGEN1181 has demonstrated meaningful clinical activity across various tumor types and treatment settings.

Rationale for Design, Dose Selection, and Treatment Schedule

Participants will receive VBI-1901 vaccine (optimal dose of 10 µg pp65 content) administered with 200 µg GM-CSF every 4 weeks until clinical disease progression. This dose schedule is consistent with data demonstrating that vaccinating more frequently than monthly can antagonize vaccine-induced immunity[23]. Because frequencies of memory HCMV-specific CD4+ and CD8+ T cells in healthy, asymptomatic participants are among the highest associated with any viral infection[24] the first immunization with VBI-1901 is anticipated to maximize the immunological response both by increasing the number of HCMV-specific CD4+ and CD8+ T cells and by converting memory cells into effector cells. Subsequent monthly vaccinations are intended to maintain high frequencies of effector T cells.

It is now well established that tumor-specific T cells can become "exhausted" due to chronic stimulation, and that blockade of PD-1 expression on such T cells can prolong their activity and confer clinical benefit in a variety of solid human tumors[25]. Balstilimab has demonstrated promising and durable clinical activity in patients with recurrent/metastatic cervical cancer[26]. Whereas vaccination with VBI-1901 is expected to restimulate CMV-specific T cells that can recognize and eliminate tumor cells in participants, concurrent and on-going administration of balstilimab is anticipated to sustain the activity of the anti-tumor response induced with VBI-1901.

Potential Risks and Benefits

Potential Risks

Successful therapy after vaccination with VBI-1901 may result in transient inflammatory reactions in the central nervous system (CNS) as with other modalities targeting other tumor antigens expressed by glioblastoma (GBM) tumor cells. In addition, off-target CNS AEs (e.g., increased cranial pressure, new neurological deficit, or changes in cognitive function) might also be observed as a result of a potential HCMV viremia. However, vaccination against HCMV in participants with primary GBM, or adoptive transfer of HCMV-specific T cells to participants with recurrent GBM, has not elicited any significant toxicity in early clinical trials with encouraging signs of clinical benefit[9].

Preclinical studies in mice and rabbits have demonstrated no evidence of inherent toxicity associated with VBI-1901, and this has been confirmed in HCMV+ rhesus macaque monkeys vaccinated with a monkey-specific version of VBI-1901 with no evidence that boosting of HCMV-specific immunity induced immune-mediated toxicity.

Extensive clinical safety experience has been generated with balstilimab and several other PD-1 pathway–blocking monoclonal antibodies to-date[27,28]. Potential risks of exposure to balstilimab include infusion-related reactions and an increase in immune-related adverse events (irAEs), which constitute a unique spectrum of AEs that occur via activation of the subject's immune system and

that can sometimes lead to serious and even fatal events[27,28]. irAEs are events that are drug-related and can be explained by an immune phenomenon after other etiologies have been ruled out.

The VBI-1901 vaccine, adjuvant GM-CSF, and anti-PD-1 mAb balstilimab have all been investigated in clinical studies previously.

Potential Benefits

Immunotherapy targeting HCMV antigens expressed by GBM tumors could help control residual disease after tumor resection, improving quality of life, progression free survival, and overall survival.

The importance of immune surveillance in controlling outgrowth of neoplastic transformation is well described and consistent with a correlation between prevalence of tumor-infiltrating lymphocytes in cancer tissues and favorable prognosis in various malignancies[31]. Inhibition of the PD-1 pathway by blockade of receptor-ligand interactions has been demonstrated to improve clinical outcome in a range of malignancies. Blockade of PD-1 in the presence of balstilimab is expected to improve anti-tumor responses and tumor control via immune-mediated mechanisms.

2. PARTICIPANT SELECTION

2.1 Eligibility Criteria Specific to the VBI-1901/Balstilimab (AGEN2034) Arm

Participants must meet all eligibility criteria outlined in the master protocol (section 3) and complete initial registration (section 4 of master protocol). Once the randomization assignment has been received following initial registration, all participants randomized to the VBI-1901/balstilimab arm must meet the following criteria prior to participating in the VBI-1901/balstilimab arm of the study.

Participants must be willing and able to provide written informed consent for the VBI-1901/balstilimab arm of the INSIGhT trial.

2.2 Second INSIGhT Registration: Registration to VBI-1901/Balstilimab Arm

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore®. Registration to the VBI-1901/balstilimab arm must occur following initial registration to master INSIGhT protocol and receipt of randomization assignment, and prior to the initiation of protocol therapy. Any participant not registered to their protocol specific assigned arm before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria in section 0of this sub-study appendix and a member of the study team will complete the protocol-specific eligibility checklist.

Following initial registration, any additional laboratory assessments prior to start of treatment will not be used to re-confirm eligibility. Refer to section 4 of this appendix for toxicity management between registration and start of study treatment.

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

Registration Process for DF/HCC Institutions

Dana-Farber/Harvard Cancer Center (DF/HCC) Standard Operating Procedure for Human Participant Research Titled *Participant Protocol Registration* (SOP #: REGIST-101) must be followed.

Registration Process for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute (DFCI) by the DFCI Coordinating Center staff. All sites should contact the DFCI Coordinating Center to verify slot availabilities. The required forms for registration can be found in Appendix B.

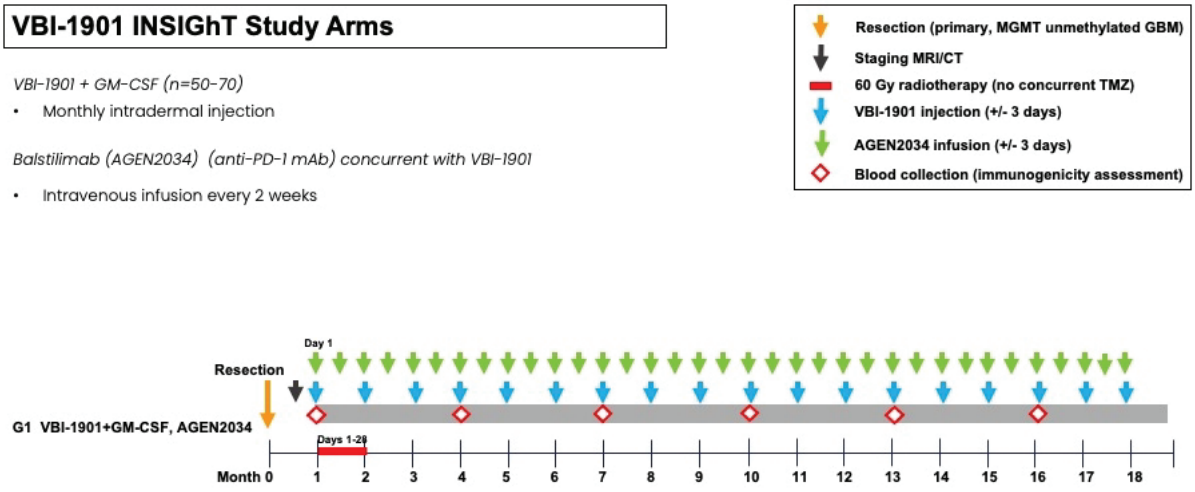
Following registration, participants should begin as soon as feasible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Refer to Appendix B, Section 3.7 for registration details.

3. TREATMENT PLAN

Participants treated on the VBI-1901/balstilimab arm will receive daily radiation (60 Gy in 30 fractions) as described in section 3.1 of this appendix, concurrent with monthly intradermal (ID) injections of VBI-1901 + GM-CSF and IV infusion every 2 weeks with balstilimab (anti-PD-1 mAb) (see Figure 3). Participants will receive adjuvant VBI-1901 + GM-CSF and Balstimimab as part of the overall protocol treatment plan. Participants will not receive either concurrent or adjuvant temozolomide.

Figure 3: VBI-1901/Balstilimab (AGEN2034) Study Arm



GBM = glioblastoma; GM-CSF = granulocyte-macrophage colony-stimulating factor; mAb = monoclonal antibody; MRI/CT = magnetic resonance imaging/computed tomography; PD-1 = programmed cell death protein 1; TMZ = temozolomide

3.1 Definition of Standard Radiation Therapy

The participant must undergo magnetic resonance imaging (MRI) based treatment planning (computed tomography [CT] with contrast-based planning only if participant unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). This volume must be treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast-enhancing region is acceptable. Treatment or no treatment of the T2/fluid-attenuated inversion recovery (FLAIR) abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 28 calendar days. Maximum dose (defined as a volume greater than 0.03 cc) to critical structures include: 60 Gy to the brainstem, 56 Gy to the optic chiasm, 55 Gy to the optic nerves, and 50 Gy to the retinae.

Participants are permitted to have radiotherapy as described in this section performed at any National Cancer Institute (NCI) funded cooperative group site. Prospective Overall PI approval is required for any radiotherapy site that is not an NCI funded cooperative group site. Any questions regarding permitted radiotherapy sites should be directed to the DFCI Coordinating Center or Overall PI Patrick Y. Wen, MD.

3.2 Treatment Regimen – VBI-1901 Administration

10 µg HCMV pp65 was determined to be the optimal dose for VBI-1901. All formulations of study vaccine will be administered ID in two sites with GM-CSF on Day 1, and then every 4 weeks (28 days ± 3 days) until clinical disease progression (see master protocol section 11.2.3) or until no longer in the best interest of the participant. The site of ID injection should be on the inner forearm, upper chest, and upper back, and will be standardized across all study sites beginning at first injection. Vaccine should be administered intradermally (ID) at two different injection sites (0.1 mL/site), 1 inch or more apart on the same selected area (e.g., inner forearm). The site of injection will also alternate each month such that sites are not injected with VBI-1901 more frequently than every 2 months. Participants will remain at the study center for

30 minutes after vaccination and will be evaluated by study center personnel for AEs before discharge and 2 weeks post vaccination.

The participants enrolled in the study will receive injections of VBI-1901 every 4 weeks until withdrawal criteria are met (toxicity, confirmed clinical disease progression, no longer in best interest of participant).

While in treatment phase, participants will receive the study vaccine every 4 weeks and will come back approximately every 2 weeks for balstilimab administration and safety assessments. Immunogenicity assessments will be conducted every 3 months (see section **Error! Reference source not found.**).

3.3 Treatment Regimen – Balstilimab Administration

The anti-PD-1 mAb balstilimab will be administered by IV infusion every 2 weeks concurrent with VBI-1901 in the outpatient setting. The first dose of balstilimab will be administered at Day 15, and then every 2 weeks until clinical disease progression (see master protocol section 11.2.3) or until no longer in the best interest of the participant, as described in section 3.2). Balstilimab will be administered using weight-based dosing of 3mg/kg. Sites should follow their institutional standard of practice for dose recalculation with weight changes.

Balstilimab should be administered via IV infusion over 30 (± 15) minutes in the VBI-1901/balstilimab arm. Patients must be observed for 10 minutes post-balstilimab infusion for infusion-related reactions. Infusions will be followed immediately with a saline flush of the IV line, per institutional guidelines. In the VBI-1901/balstilimab arm, balstilimab should be administered first. However, the treating neurooncologist may opt to administer VBI-1901 first if desired for ease/convenience of the treating neurooncologist and the patient.

3.4 Definition of Dose-Limiting Toxicity

The first subject will be immunized with 10 µg/ml VBI-1901 plus GM-CSF concurrent with IV infusion of Balstilimab, with a safety review by the study site investigators 7-10 days after the first balstilimab dose (a timeframe ensuring the peak of immune response has occurred). The safety review of the first subject will be completed prior to further administration of Balstilimab and vaccination of the subject and prior to treatment of the next study subject. Safety data obtained during the first 10 weeks of study treatment with VBI-1901 plus GM-CSF and Balstilimab from the first 6 subjects will be reviewed by a Data and Safety Monitoring Board (DSMB). If none of the six patients experiences a dose-limiting toxicity related to study drugs, then the DSMB may recommend that further subjects may be treated without the need for safety review of each subject before initiating treatment of another subject. The DSMB will also review the study every 3 months.

If > 2 of the 6 patients experiences a DLT related to study drugs the study will proceed with just VBI-1901 alone without Balstilimab.

A DLT is defined as a clinically significant AE considered at least possibly related to VBI-1901 or balstilimab and meets any of the criteria below during the first 10 weeks of study treatment

(referred to as the concomitant/initiation cycle). If a participant comes off for reasons other than a dose-limiting toxicity during the DLT period, he/she will be replaced.

Dose limiting toxicities are defined below. A DLT must have an attribution of possible, probable, or definite to VBI-1901 or balstilimab and meet the below criteria. If there is any question concerning a DLT, sites should contact the DFCI Coordinating Center to determine participant's DLT status. The Coordinating Center with the Overall PI will make the final decision.

- Hematological toxicities will be considered dose limiting if any of the following occur (grade 3 or 4 lymphopenia will not be considered a DLT):
    - Absolute neutrophil count (ANC) of < 500/mm^3 for > 7 days
    - Platelets < 25,000/mm^3 for > 48 hours or platelets < 50,000/mm^3 with clinically significant bleeding
    - ≥ Grade 3 febrile neutropenia (ANC < 1.0 × 10^9/L and fever > 101°F/38.3°C)
    - Any hematologic toxicity that prevents administration of VBI-1901 or balstilimab for > 28 days
- Non-hematological toxicities will be considered dose limiting if any of the following occur:
    - Inability to complete ≥ 75% of radiotherapy due to toxicity related to or exacerbated by VBI-1901 or balstilimab added to Radiation Therapy.
    - Hy's Law (elevated ALT or AST by 3-fold or greater above the upper limit of normal together with elevation of their serum total bilirubin of greater than 2× the upper limit of normal, without findings of cholestasis and no other explanation for these elevations)
    - Grades 3-4 severity, with the following exceptions:
        - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
        - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
        - Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis
        - Grade 3 fatigue for greater than 1 week

Death

The occurrence of any Grade 5 event or any two Grade 4 events considered at least possibly related to VBI-1901 or balstilimab and unexpected with VBI-1901 or balstilimab will trigger suspension of accrual and performance of a thorough safety review prior to resuming enrollment.

3.5 General Concomitant Medication and Supportive Care Guidelines

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

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

- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Participants should stop using any herbal medications 7 days prior to first dose of study drug.
- Immunosuppressants other than corticoids, are not allowed in the study.
- Febrile neutropenia may be managed according to the local institution's guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the participant observed.
- Granulocyte colony-stimulating factor (G-CSF): Routine prophylactic use of G-CSF is not permitted, except as indicated in the study protocol. However, therapeutic use in participants with serious neutropenic complications, such as sepsis, may be considered at the investigator's discretion.
- Pneumocystis jiroveci pneumonia (PJP) prophylaxis: Since participants with GBM are at increased risk of developing PJP, especially if they are on corticosteroids, prophylaxis for PJP may be considered per institutional practice.
- Surgery: If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the operative note, and pathology report.
- Other anticancer or experimental therapies: No other experimental anticancer therapy of any kind is permitted during the study treatment period. No other drug under investigation may be used concomitantly with the study drug.
- Other concomitant medications: Therapies considered necessary for the well-being of the participant may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded.

Rescue Medications, Treatments, and Procedures

Participants will be closely monitored. Any signs of brain edema will be rapidly observed and therapeutic options will be provided. Of note, successful therapy after vaccination with VBI-1901 might result in transient inflammatory reactions in the CNS as with other modalities targeting other tumor antigens expressed by GBM tumor cells. If the participant requires hospitalization for presumed treatment-related effect, then the local clinician may give up to 8 mg dexamethasone to treat brain edema. Increased cranial pressure, new neurological deficit, or changes in cognitive function not responsive to up to 8 mg dexamethasone will require immediate imaging and, if any evidence of involvement of the brain outside of the region of tumor, treatment with ganciclovir and higher dose steroids to eliminate any potential HCMV viremia and inflammatory immune response that might be responsible for the observed AEs.

3.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. In the absence of treatment delays due to AE(s), treatment may continue on the VBI-1901/balstilimab arm until one of the following criteria applies:

- Disease progression (see section 11 of main INSIGhT protocol)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Cases of pregnancy that occur during maternal exposures to VBI-1901/balstilimab either directly or through exposure of partner should be reported. If a participant is determined to be pregnant following VBI-1901/balstilimab initiation, she must discontinue study treatment immediately. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and product safety evaluation (see section 0).

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

An Office of Data Quality (ODQ) Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Patrick Y. Wen, MD, at 617-632-2166 or pwen@partners.org.

3.7 Duration of Follow Up

Participants will be followed until death with scheduled clinic visits, telephone contact, or medical record review. Participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE. Refer to section **Error! Reference source not found.** study calendar within this appendix for follow-up requirements and time points.

3.8 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the CRF.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

4. DOSING DELAYS/DOSE MODIFICATIONS

No modifications of VBI-1901 are planned to adjust a participant's dose. If an ID injection is imperfect (e.g., subcutaneous injection) then it will be documented but no additional vaccine will be administered. If the investigator or qualified designee determines that the participant's health on the day of administration temporarily precludes administration, the visit will be rescheduled within the allowed interval for this visit (+/-3 days).

No dose reductions are allowed for balstilimab. Each patient will stay on the dose levels assigned in the trial unless treatment needs to be stopped. Intra-patient dose reductions or dose escalations of balstilimab are not permitted.

4.1 Anticipated Toxicities

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

Anticipated Toxicities for Radiation Therapy

A list of AEs of all grades suspected to be radiation therapy treatment related, organized by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 category, includes:

- EAR AND LABYRINTH DISORDERS – external ear inflammation; other: dryness of ear canal; other: hardening of ear canal wax; external ear pain; other: hearing loss
- ENDOCRINE DISORDERS - other: hypophysitis, or hypopituitarism
- EYE DISORDERS – cataract; other: decreased vision
- GASTROINTESTINAL DISORDERS – nausea; vomiting
- GENERAL DISORDERS – fatigue
- INJURY, POISONING AND PROCEDURAL COMPLICATIONS – injury other: optic nerve
- INVESTIGATIONS –lymphocyte count decreased
- MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS – generalized muscle weakness
- NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED – treatment related secondary malignancy
- NERVOUS SYSTEM DISORDERS – headache; seizure; memory impairment; cognitive disturbance; somnolence; dysgeusia; central nervous system necrosis
- PSYCHIATRIC DISORDERS – personality change
- SKIN AND SUBCUTANEOUS TISSUE DISORDERS – scalp pain; other: scalp redness; alopecia

Suspected & Anticipated Toxicities for VBI-1901 and GM-CSF

A list of AEs of all grades suspected to be VBI-1901 treatment related according to review of the Investigator's Brochure, experience with other drugs in the same class, and preclinical data, includes:

Very Common (≥10%):

- Injection site pain
- Injection site erythema
- Injection site pruritus
- Fever
- Fatigue
- Headache
- Nausea
- Myalgia
- Arthralgia

Common (1-10%):

- Injection site induration
- Injection site rash
- Chills
- Vomiting

Some participants taking GM-CSF (LEUKINE®) may experience unwanted side effects, most of which are mild to moderate and not serious.

Some of the more common side effects include bone pain, feeling like participant has the flu, feeling tired or weak, muscle aches, diarrhea, or stomach upset. Participants may also get a low fever (less than 100.5°F or 38°C) about 1 to 4 hours after an injection, or they may have swelling, redness, and/or discomfort where GM-CSF is injected.

Some side effects or symptoms may be serious. These may be due to GM-CSF, the underlying illness, or other treatments participants may have received.

Participants will be instructed to contact the study team immediately if:

- They develop a high fever (over 100.5°F or 38°C).
- They notice any signs of infection including chills, sore throat, or congestion (such as a stuffy nose).
- They have trouble breathing, or develop wheezing, fainting, extensive skin rash, hives, or feel they are having an allergic reaction.
- They experience sudden weight gain or other signs of fluid build-up such as swollen legs or feet.
- They develop chest pain, chest discomfort, or a rapid or irregular pulse.

Suspected & Anticipated Toxicities for Balstilimab

Immuno-oncology agents such as balstilimab are associated with irAEs. Early recognition and management of irAEs may mitigate severe toxicity. A list of irAEs of all grades suspected to be balstilimab treatment related are reviewed in the Investigator's Brochure. Investigators should monitor patients closely for potential irAEs, which may manifest at the earliest after weeks of treatment. Such events may consist of persistent rash, diarrhoea, colitis, encephalitis, arthritis, endocrine disorders, cardiomyopathy, or uveitis and other inflammatory eye conditions, among others. Management algorithms have been developed to assist Investigators in assessing and managing the following groups of irAEs: gastrointestinal, pulmonary, dermatological, renal, hepatic, neurological, and endocrine, among others.

AEs (both nonserious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These irAEs may be predicted based on the nature of the study drugs, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of study drug. Particular attention should be paid to AEs that may be suggestive of potential irAEs.

4.2 Immune Related Management Guidelines

Dermatological Immune-Related Adverse Events

Rule out non-immune causes, if non-immune cause is identified, treat accordingly, and continue therapy.

Table 2: Dermatological Immune-Related Adverse Event Management Algorithm

Dermatological Immune-Related Adverse Events		
Grade of Rash (NCI- CTCAE v5.0)	**Management**	**Follow-Up**

Grade 1–2 Covering ≤ 30% body surface area.	• Symptomatic therapy (eg, antihistamines, topical corticosteroids). • Continue BAL therapy per protocol.	• If persists > 1 to 2 weeks or recurs, consider skin biopsy. • Delay BAL therapy. • Consider 0.5 to 1 mg/kg/day methylprednisolone intravenous (IV) or oral equivalent. Once improving, taper corticosteroids over at least 1 month; consider prophylactic antibiotics for opportunistic infections; and resume BAL therapy per protocol. • If worsens: treat as Grade 3–4.
Grade 3–4 Covering > 30% body surface area; life-threatening consequences.	• Discontinue BAL therapy per protocol. • Consider skin biopsy. • Dermatology consult • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent.	

Abbreviations: BAL: balstilimab; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Gastrointestinal Immune-Related Adverse Events

Rule out non-immune causes, if non-immune cause is identified, treat accordingly, and continue therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Table 3: Gastrointestinal Immune-Related Adverse Event Management Algorithm

Gastrointestinal Immune-Related Adverse Events		
Severity of Diarrhea/Colitis (NCI-CTCAE v5.0)	**Management**	**Follow-Up**
Grade 1 Diarrhea: < 4 stools/day over baseline. Colitis: asymptomatic.	• Continue BAL therapy per protocol. • Symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide for 2 to 3 days	• Close monitoring for worsening symptoms. • Educate patient to report worsening symptoms immediately. • If worsens: treat as Grade 2 or 3– 4. • Fecal lactoferrin and calprotectin can be considered to differentiate functional vs inflammatory diarrhea
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated < 24 h; not interfering with activities of daily living (ADL). Colitis: abdominal pain; blood in stool	• Delay BAL therapy per protocol. • Delay treatment per protocol. • Symptomatic treatment. • Consider gastrointestinal (GI) consult. • Work-up to rule out infectious etiology (*Clostridium difficile* toxin, stool cultures, etc.) • Consider imaging computed tomography (CT) scan of abdomen and pelvis, GI endoscopy with biopsy • If Immune Diarrhea/colitis - start methylprednisolone or equivalent with initial dose of 1 mg/kg/day	• If improves to Grade 1: resume treatment per protocol. • When symptoms improve to Grade 1, taper corticosteroids over at least 1 month; resume treatment per protocol. • If worsens or persists > 2 to 3 days with oral corticosteroids: treat as Grade 3–4. • Consider adding tumor necrosis factor (TNF)-alpha or integrin blockers.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL. Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. 4: life-threatening,	• Discontinue treatment per protocol. • Work-up to rule out alternate causes and infectious etiology • Consider imaging (CT scan of abdomen and pelvis, GI endoscopy with biopsy) • 1 to 2 mg/kg/day methylprednisolone IV or equivalent. • Consider GI consult. • Consider inpatient care. • Consider lower endoscopy. Note: Colonoscopy is contraindicated for Grade 4.	• If improves: continue corticosteroids until Grade 1, then taper over at least 1 month. • If persists >1 to 2 days or recurs after improvement: add TNF-alpha or integrin blockers. Note: The use of integrin blockers (eg, vedolizumab) may be considered in patients refractory to TNF-alpha blockers and/or contraindication to use them.

perforation		

Abbreviations: BAL: balstilimab; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Event

Pulmonary Immune-Related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol. Evaluate with imaging and pulmonary consultation.

Table 4: Pulmonary Immune-Related Adverse Event Management Algorithm

Pulmonary Immune-Related Adverse Events		
Grade of Pneumonitis (NCI-CTCAE v5.0)	**Management**	**Follow-Up**
Grade 1 Radiographic changes only.	• Consider delay of BAL therapy per protocol. • Monitor for symptoms every 2 to 3 days. • Consider pulmonary and infectious disease consults. Consider chest computed tomography (CT) with contrast.	• Re-image every ≥3 weeks. • If worsens: treat as Grade 2 or Grade 3–4.
Grade 2 Mild to moderate new symptoms	• Delay BAL therapy per protocol. • Pulmonary and infectious disease consults. • Monitor symptoms daily; consider hospitalization. • 1 mg/kg/day methylprednisolone intravenous (IV) or oral equivalent. • Consider bronchoscopy, lung biopsy.	• Re-image every 1 to 3 days. • If improves: when symptoms return to near baseline, taper corticosteroids over at least 1 month, then resume BAL therapy per protocol, and consider prophylactic antibiotics. • Consider chest CT with contrast. • If not improving after 2 to 3 days of corticosteroids: treat as Grade 3–4.
Grade 3–4 Severe new symptoms; new/ worsening hypoxia; life- threatening.	• Discontinue BAL therapy per protocol. • Hospitalize. • Pulmonary and infectious disease consults. • 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider bronchoscopy, lung biopsy.	• If improves to baseline: taper corticosteroids over at least 6 weeks. • If not improving after 48 hours or worsening: add additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

Abbreviations: BAL: balstilimab; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Hepatic Immune-Related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol. Consider imaging for obstruction.

Table 5: Hepatic Immune-Related Adverse Event Management Algorithm

Hepatic Immune-Related Adverse Events		
Grade of Liver Test Elevation (NCI-CTCAE v5.0)	**Management**	**Follow-Up**
Grade 1 AST or ALT >upper limit of normal (ULN) to 3 × ULN	• Continue BAL therapy per protocol with close monitoring.	• Continue liver function tests (LFT) monitoring 1 to 2 times/week • If worsens: treat as Grade 2 or Grade 3–4.
Grade 2 AST or ALT >3 to ≤5 × ULN	• Delay BAL therapy per protocol. • Increase frequency of monitoring to every 3 days. • Patients should stop unnecessary medications, known hepatotoxic drugs and alcohol consumption	• If returns to baseline: resume routine monitoring; resume BAL therapy per protocol. • If elevations persist > 5 to 7 days or worsen**:** 0.5 to 1 mg/kg/day methylprednisolone intravenous (IV) or oral equivalent. When liver function tests (LFT) return to Grade 1 or baseline, taper corticosteroids over at least 1 month, consider prophylactic antibiotics for opportunisticinfections, and resume BAL therapy per protocol.
Grade 3–4 AST or ALT >5 × ULN	• Consider discontinuation of BAL perprotocol. • Increase frequency of monitoring to every 1 to 2 days. • 1 to 2 mg/kg/day methylprednisolone intravenous IV or oral equivalent*. • Inpatient care and hepatology consult. • Consider obtaining magnetic resonance imaging/computed tomography scan of liver and liver biopsy ifclinically warranted.	• If returns to Grade ≤ 2**:** taper corticosteroids over at least 1 month. • If corticosteroid refractory or does not improve in 3 days: consider mycophenolate mofetil (0.5 to 1 g every 12 hours). If returns to Grade ≤ 1 and after completion of a steroid taper, consider stopping mycophenolate at the same time**.** • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

AST or ALT >3 ULN + Bilirubin >2 × ULN	• Discontinue BAL per protocol. • Consider inpatient care • LFT monitoring every 2 to 3 days • 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent. Patients should stop unnecessary medications, known hepatotoxic drugs and alcohol consumption • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	• If returns to Grade ≤ 1: taper corticosteroids after at least 1 month of full cycle treatment • If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil (0.5 to 1 g every 12 h). If returns to Grade ≤ 1 and after completion of steroid taper, consider stop of mycophenolate at the same time. Anti-tumor necrosis factor-alfa agents should not be used for hepatitis.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BAL: balstilimab; CT: computer tomography; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

*The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrine Immune-Related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol. Consider visual field testing, endocrinology consultation, and imaging.

Table 6: Endocrine Immune-Related Adverse Event Management Algorithm

Endocrine Immune-Related Adverse Events		
Endocrine Disorder	**Management**	**Follow-Up**
Asymptomatic hypothyroidism	• Continue BAL therapy per protocol. • Monitor thyroid stimulating hormone (TSH), free thyroxine (FT4) every 4 to 6 weeks • If TSH >10 or normal/high TSH and low FT4 consider oral levothyroxine at approximately 1.6 mcg/kg daily until TSH returns to normal levels	• Once adequately treated, monitor thyroid function every 4 to 6 weeks while on BAL, or as needed for symptoms • Extreme elevations of TSH can be seen in the recovery phase of thyroiditis and can be watched in asymptomatic patients to determine whether there is recover to normal within 3 to 4 weeks
Symptomatic hypothyroidism	• Continue BAL therapy per protocol. • Monitor TSH every 4 to 6 weeks • Endocrine consultation • Start oral levothyroxine at approximately 1.6 mcg/kg daily until TSH returns to normal levels • Exclude concomitant adrenal insufficiency	• Once adequately treated, monitor thyroid function every 4 to 6 weeks while on BAL, or as needed for symptoms • Adrenal dysfunction, if present, must always be replaced before thyroid therapy is initiated.
Hyperthyroidism	• Endocrine consultation if symptomatic • Consider b-Blocker (eg, atenolol, propranolol) for symptomatic relief. • Restart therapy when Grade ≤ 2. • Check thyroid functions every 2 to 3 weeks. • If Graves' disease, treat with methimazole or radioactive iodine / surgery. • For severe symptoms or concern for thyroid storm	• Monitor thyroid function every 4 to 6 weeks • If resolved, not further treatment for hyperthyroidism • Hyperthyroidism often evolves to hypothyroidism which will require thyroid hormone therapy. • In case of steroid therapy - when symptoms return to near baseline, taper corticosteroids over 1 to 2 weeks.

Endocrine Immune-Related Adverse Events		
Endocrine Disorder	**Management**	**Follow-Up**
	hospitalize patient and initiate prednisone 1 to 2 mg/kg/day or equivalent	
Hypophysitis	• Delay protocol treatment until patient is stabilized on replacement hormones. • Evaluate ACTH, cortisol (AM), TSH, FT4. • Consider brain magnetic resonance imaging (MRI) ± contrast with pituitary/sellar cuts if symptomatic. • Endocrine consultation. • Consider visual field testing, hormonal supplementation as needed (for hypothyroidism, adrenal insufficiency). • In case of acute severe symptoms, carefully consider prednisone 1 to 2 mg/kg oral daily or intravenous (IV) until symptoms resolve.	• Follow FT4 for thyroid hormone replacement titration. • Always start corticosteroids first (if needed) when planning hormone replacement therapy. • In case of steroid therapy, when symptoms return to near baseline, taper corticosteroids over at least to 2 weeks. • Patients with adrenal insufficiency may need to continue corticosteroids with mineralocorticoid component. • No abnormal laboratory tests and/or pituitary MRI scan but symptoms persist: Repeat laboratory tests in 1 to 3 weeks, MRI in 1 month.
Suspicion of adrenal crisis (eg, severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue BAL therapy per protocol. • Rule out sepsis. • Stress dose of IV corticosteroids with mineralocorticoid activity. • IV fluids. • Consult endocrinologist. • If adrenal crisis ruled out, patients with adrenal insufficiency may need to continue corticosteroids with mineralocorticoid component.	

Abbreviations: ACTH: adrenocorticotropic hormone; BAL: balstilimab.

Renal Immune-Related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol.

Table 7: Renal Immune-Related Adverse Event Management Algorithm

Renal Immune-Related Adverse Events		
Grade of Creatinine Elevation (NCI-CTCAE v5.0)	**Management**	**Follow-Up**
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5× baseline.	• Continue BAL per protocol. • Monitor creatinine weekly	• If returns to baseline: resume routine creatinine monitoring per protocol. • If worsens: treat as Grade 2 or Grade 3–4.
Grade 2-3 Creatinine > 1.5 × baseline to ≤ 6 × ULN.	• Delay BAL per protocol. • Rule-out alternate cause • Monitor creatinine every 2 to 3 days • Follow urine protein/ creatinine ratio every 3 to 7 days. • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. • Consider renal biopsy	• If returns to Grade 1: taper corticosteroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume BAL and routine creatinine monitoring per protocol. • If elevations persist > 7 days or worsen: treat as Grade 4.
Grade 4 Creatinine > 6 × ULN.	• Discontinue BAL therapy per protocol. • Monitor creatinine daily. • 1.0 to 2.0 mg/kg/day methylprednisolone intravenous (IV)or IV equivalent. • Consult nephrologist. • Consider renal biopsy	• If returns to Grade 1: taper corticosteroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. • If kidney injury remains Grade > 2 after 4 to 6 weeks of steroids consider adding one of the following: azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, tumor necrosis factor -alpha blockers.

Abbreviations: BAL: balstilimab; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse events.

Neurological Immune-Related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly, and continue therapy per protocol.

Table 8: Neurological Immune-Related Adverse Event Management Algorithm

Neurological Immune-Related Adverse Events		
Grade of Neurological Toxicity (NCI CTCAE v5.0)	**Management**	**Follow-Up**
Grade 1 Asymptomatic or mild symptoms; intervention not indicated.	• Continue BAL therapy per protocol.	• Continue to monitor patient. • If worsens: treat as Grade 2 or Grade 3–4.
Grade 2 Moderate symptoms; Limiting instrumental activities of daily life (ADL).	• Delay BAL therapy per protocol. • Treat symptoms per local guidelines. • Consider 0.5 to 1.0 mg/kg/day methylprednisolone intravenous (IV) or oral equivalent.	• If returns to baseline: resume BAL therapy per protocol. • If worsens: treat as Grade 3 to 4.
Grade 3-4 Severe symptoms; limiting self-care activities of daily life; life- threatening.	• Discontinue BAL therapy per protocol. • Obtain neurology consult. • Treat symptoms per local guidelines. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections.	• If improves to Grade 2: taper corticosteroids over at least 1month. • If worsens or atypical presentation: consider IV immunoglobulin or other immunosuppressive therapies per local guidelines.

Abbreviations: BAL: balstilimab; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

4.3 Dose Modifications/Delays for Balstilimab

Immune checkpoint inhibitors (ICIs), such as Balstilimab, are the standard of care for the treatment of several cancers. While these immunotherapies have improved patient outcomes in many clinical settings, they bring accompanying risks of toxicity, specifically immune-related adverse events (irAEs). While management varies according to the organ system affected, in general, no dose reductions are allowed. Each patient will stay on the dose level and/or combination assigned in the trial unless treatment needs to be stopped. Balstilimab therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities. Therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert to grade 1. Corticosteroids may be administered. Grade 2-4 toxicities would warrant suspension of Balstilimab and the initiation of high-

dose corticosteroids. Corticosteroids should be tapered over the course of at least 4-6 weeks. Some refractory cases may require other immunosuppressive therapy. In general, permanent discontinuation of Balstilimab is recommended with grade 3-4 toxicities, except for endocrinopathies that have been controlled by hormone replacement. More specific treatment guidelines based on organ system and toxicity diagnosis, updated by ASCO in 2021, can be found here:https://ascopubs.org/doi/full/10.1200/JCO.21.01440.

4.4 Potential Overlapping Toxicities From Radiotherapy, VBI-1901 and Balstilimab

While the toxicities from radiotherapy, VBI-1901, and Balstilimab are largely non-overlapping, cerebral edema and fatigue are potentially overlapping toxicities.

Cerebral edema

Grade 3 or greater cerebral edema developing during irradiation should be treated with high dose corticosteroids per institutional guidelines and all treatment should be held until improvement to baseline. Radiotherapy, VBI-1901 and Balstilimab may be resumed together with corticosteroids. If grade 3 cerebral edema recurs, VBI-1901 and balstilimab should be discontinued. When clinically safe, radiotherapy should be resumed with corticosteroids to complete the course of treatment.

Grade 3 or greater cerebral edema during treatment with VBI-1901 and Balstilimab should be treated with high dose corticosteroids per institutional guidelines and all treatment should be held until improvement to baseline. VBI-1901 and Balstilimab may be resumed together with corticosteroids. If grade 3 cerebral edema recurs, VBI-1901 and balstilimab should be discontinued.

Fatigue

Fatigue is common in patients receiving radiotherapy and to a lesser extent Balstilimab.

During radiotherapy, patients with grade 3 or greater fatigue should have all treatment held until recovery to grade 2 when treatment may be resumed.

During treatment with VBI-1901 and Balstilimab alone, patients with grade 3 or greater fatigue should have all treatment held until recovery to grade 2 when treatment may be resumed. If grade 3 fatigue recurs Balstilimab will be discontinued. VBI-1901 may be continued.

5. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event monitoring and reporting is a routine part of every clinical trial. Safety data including solicited and unsolicited AEs and laboratory tests results will be obtained from the first injection until the final study visit. The following list of reported and/or potential AEs (section 4.1 of this appendix) and the characteristics of an observed AE (section 0 of this appendix) will determine whether the event requires expedited reporting **in addition** to routine reporting.

This section specifies reporting requirements to the Food and Drug Administration (FDA), Overall PI/Coordinating Center, DF/HCC Institutional Review Board (IRB), and manufacturer as applicable.

5.1 Expected Toxicities

Refer to section 4.1 of this appendix for expected toxicities for assigned study treatment arm.

5.2 Adverse Event Characteristics

- **Adverse Event (AE) Definition:**
  An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing AE related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized or determined to be irreversible by an investigator.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed in section 4.1 of this appendix should be reported only if the AE varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

- **Serious Adverse Event (SAE) Definition:**

A SAE is any AE, occurring at any dose and regardless of causality that:

  - Results in death
  - Is life-threatening (i.e., in the opinion of the Investigator, the participant is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the participant's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event. Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

5.3 Solicited Adverse Events

Adverse events in this list will be monitored after each injection of VBI-1901. They will be assessed for severity and seriousness and recorded in the CRF.

- Injection Site Reaction
  - Pain (pain without touching) at injection site;
  - Tenderness (pain when area is touched) at injection site;
  - Erythema/redness at injection site;
  - Swelling at injection site;
  - Induration at site injection;
  - Itching at injection site.

For injection site reactions: it is permitted to add an ice pack to injection sites for redness, swelling, and pain, if needed. If further treatment is required, a topical antihistamine is permitted.

Systemic Reaction

- Fever (oral temperature > 37.6 C);
- Chills;
- Arthralgia;
- Headache;
- Myalgia;
- Nausea;
- Vomiting;
- Fatigue/Asthenia;
- Acute systemic allergic reaction;
- Rash.

Grading of Local Solicited Adverse Events

Solicited AEs for VBI-1901 will be graded according to the FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007) - see section 9.

Reactogenicity

Reactions to vaccine will be assessed 30 minutes following each immunization and during the 28 following days. Reactions to vaccine will be assessed at each visit and recorded in the CRF for the corresponding visit. If a reaction to vaccine meets the criteria of an SAE, the investigator or delegates will complete and submit an SAE report form (see also section 0).

For the purpose of standardizing recording of local reactions:

- The largest diameter of redness or swelling at the injection site will be recorded.
- Study participants will be asked to indicate the maximum pain they experience at the injection site on a scale from 0 to 3 (0: no pain 1: Mild discomfort to touch 2: Discomfort with movement 3: Significant discomfort at rest).

For injection site reactions: it is permitted to add an ice pack to injection sites for redness, swelling, and pain if needed. If further treatment is required, a topical antihistamine is permitted.

5.4 Expedited Adverse Event Reporting

Investigators must report to the Overall PI any SAE that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment.

For multi-institution studies where a DF/HCC investigator is serving as the Overall PI, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event that is *Serious, Unexpected,* and there is a *Reasonable Possibility* (i.e., possible, probable, or definitive attribution) the Adverse Event is related to the study intervention.

Expedited Reporting Guidelines to Overall PI/Coordinating Center & Drug Company

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites outside of DF/HCC will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting AEs. A copy of the AE form should be forwarded to the Overall PI within the timeframes detailed in the table below. The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to the DFCI IRB policies and procedures in reporting AEs.

In addition to local IRB reporting policies, all sites are required to follow **Error! Reference source not found.** expedited reportable AE requirements:

Table 9 Expedited AE Reporting Requirements to VBI Vaccines Inc. & DFCI Coordinating Center

Adverse Event Characteristics				Reporting Requirement	
Seriousness	**Toxicity**	**Known Correlation[f]**	**Attribution to VBI-1901/Balstilimab**	**VBI Vaccines Inc. - Via Fax or email[c] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**	**Overall PI (Patrick Y. Wen, MD) at the DFCI Coordinating Center Via Email [b] Use Reportable AE Coversheet [c] and Medwatch 3500A [d]**
Serious[e]	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [a]	Within 24 hours from notification [a]
Non-Serious	Grade 4	Any (Expected or Unexpected)	Any	Not Required	Within 5 working days from notification [a]
Non-Serious	Grade 2 or 3	Unexpected	Possible, probable, definite	Not Required	Within 7 working days from notification [a]

g. In the event that the participating investigator/site team does not become aware of an adverse event requiring expedited reporting immediately (e.g., participant sought treatment elsewhere), the participating investigator/site team is to report the event within the required hours/days noted above after learning of it and document the time of his or her first awareness of the adverse event. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE or reportable AE is required.
h. Email the Medwatch 3500A form, reportable AE coversheet (section 0 of this appendix), and the local IRB SAE report (if applicable) to the DFCI Coordinating Center with the participant title as "INSIGHT SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Patrick Y. Wen, and to the DFCI Coordinating Center personnel.
i. Reportable AE Coversheet is found in section 0 of this appendix. The coversheet contains all FAX numbers/e-mails and needed for reporting purposes.
j. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm
k. Seriousness is defined in section 0 of this appendix.
l. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Anticipated Toxicities list (protocol section 4.1 of this appendix) which is derived from the Investigator's Brochure.

How to report expedited AEs to VBI Vaccines Inc. & DFCI Coordinating Center/Overall PI

1. Document/describe reportable AE(s) on the following:
   a. MedWatch 3500A
   i. downloadable form at http://www.fda.gov/medwatch/getforms.htm
   b. DFCI Reportable AE Coversheet – INSIGhT VBI-1901/balstilimab Arm
   i. Coversheet can be found in section 0 of this appendix. The coversheet contains contact information for DFCI Coordinating Center and VBI Vaccines Inc. safety groups. A modifiable Microsoft Word document is also available from the DFCI Coordinating Center.

2. Scan and email above documents to NeuroOnc_SAE@dfci.harvard.edu with the participant title "INSIGHT SAE"
   a. All AE reports received at this account are forwarded immediately to Overall PI (Dr. Patrick Y. Wen), and to Coordinating Center personnel.
   b. If available and applicable, also include the local IRB submission for this event in the submission to the DFCI Coordinating Center.

Protocol-Specific Expedited Adverse Event Reporting Exclusions

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

- Lymphopenia (grades 2-4).
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Elective surgery, planned prior to signing consent
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Hospitalization for respite care not associated with an AE attributed to the study drug
- Hospitalization for treatment of participant's underlying disease after coming off study treatment (e.g. admission after participant is removed from active study treatment for craniotomy)

Expedited Reporting to the Food and Drug Administration (FDA)

As study sponsor, the Overall PI (or his designee) will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious AE that meets the FDA's criteria for expedited reporting following the reporting

requirements and timelines set by the FDA.

Expedited Reporting to Hospital Risk Management

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

Routine Adverse Event Reporting

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

Other Reporting Requirements

Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) in either a female participant or a partner of a male participant occurring while the participant is on investigational product (IP), or within 28 days of the participant's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately and the participant instructed to return any unused VBI-1901 and balstilimab. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Drug Company Drug Safety immediately by facsimile, or other appropriate method, using the Initial Pregnancy Report Form.

The female may be referred to her obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female participant until completion of the pregnancy, and must notify Drug Company Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form as a follow-up to the initial pregnancy report.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus must be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Drug Company Drug Safety immediately by facsimile, or other appropriate method, within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Drug Company Drug Safety immediately by facsimile, or other appropriate method, within 24 hrs of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Participants

If a female partner of a male participant taking investigational product becomes pregnant, the male participant taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Overdose

Overdose, as defined for this protocol, refers to balstilimab dosing only.

On a per dose basis, an overdose is defined as a dose of balstilimab at any amount over the protocol-specified dose assigned to a given participant, regardless of any associated AEs or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Notify the DFCI Coordinating Center at NeuroOnc_SAE@dfci.harvard.edu of any potential overdose as soon as possible.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33 that an annual report is provided to the FDA within 60 days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to VBI Vaccines Inc. as a supporter of this study as follows:

VBI Vaccines Inc.
310 Hunt Club Road East
Ottawa, ON K1V 1C1
Canada
Tel: (613) 749-4200

6. PHARMACEUTICAL INFORMATION

6.1 VBI-1901

Description

VBI-1901 is an eVLP vaccine that has been formulated with GM-CSF. VBI-1901 consists of a suspension of eVLPs that express HCMV gB glycoprotein on the surface of the particle

membrane and the HCMV pp65 protein in the interior of the VLP. The VBI-1901 formulation contains 10 mM sodium phosphate and 8% sucrose at pH 7. The particles are produced in HEK 293 mammalian cells transfected with the MLV gag gene and the HCMV gB and pp65 genes. Cell culture supernatants are collected and eVLPs purified by filtration, diafiltration, and anion exchange chromatography. VBI-1901 eVLPs are formulated with GM-CSF adjuvant just prior to injection. VBI-1901 is stable for at least 33 months when stored at -80°C±10°C.

Form

VBI-1901 is comprised of gB/pp65 eVLPs in an 8% sucrose solution with an opaque to milky appearance.

VBI-1901 will be supplied as vials of final drug product (FDP) comprised of gB/pp65 eVLPs at a dose of approximately 50 µg pp65/mL, in an 8% sucrose solution with an opaque to milky appearance.

VBI-1901 will be compounded at the hospital pharmacy with lyophilized GM-CSF (Leukine®), also supplied by the sponsor (see sections 0), as summarized below in section 0, and detailed in the Pharmacy Manual.

Storage and Stability

gB/pp65 eVLPs should be stored frozen at -80°C±20°C and are stable for at least 33 months, based on in-house stability study 19CH26. Additional stability data will be provided as it becomes available.

Compatibility

There are no known compatibility issues.

Handling

Routine vaccine and chemotherapy handling is recommended.

Availability

VBI-1901 is an investigational agent and will be supplied free-of-charge from VBI Vaccines Inc.

Preparation

VBI-1901 optimal dose (10 µg pp65 content) will be formulated with GM-CSF (200 µg). The study product will be compounded at the hospital pharmacy, under aseptic conditions according to a Pharmacy Manual provided by the Sponsor.

For preparation of VBI-1901 (≥50 µg/mL of pp65) with GM-CSF (Leukine® lyophilized powder, 250 µg) study sponsor will supply four different types of vials for the compounding of the

optimal dose. The first type of vial will contain VBI-1901 final drug product (2 vials needed). The second type of vial will contain 10 mL of sterile 0.9% normal saline. A third type of vial will be an empty, sterile 10 mL vial. The fourth type of vial will contain GM-CSF (Leukine® lyophilized powder, 250 µg) (2 vials needed).

For the final admix formulation, an appropriate volume of VBI-1901 and 0.9% normal saline need to be added to the empty supplied vial. Then reconstitute separately 2 vials of lyophilized GM-CSF with 250 µL each of diluted VBI-1901 (50 µg/mL). After swirling for 30±10 seconds, withdraw 0.1 mL from each of the admixed formulation and administer in separate sites ID.

Only vials supplied by the sponsor should be used to compound the study product.

Administration

VBI-1901 will be administered in two equal ID injection in two sites with GM-CSF at Day 1, and then every 4 weeks (28 days ± 3 days) until clinical disease progression (see mater protocol section 11.2.3) or until no longer in the best interest of the participant, as described in section 3.2). In the VBI-1901/balstilimab arm, balstilimab should be administered first. However, the treating neurooncologist may opt to administer VBI-1901 first if desired for ease/convenience of the treating neurooncologist and the patient.

6.2 GM-CSF (Lyophilized Leukine®)

Description

GM-CSF (LEUKINE®; sargramostim) is a recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast (*S. cerevisiae*) expression system. GM-CSF is a hematopoietic growth factor which stimulates proliferation and differentiation of hematopoietic progenitor cells.

Form

Lyophilized LEUKINE® is available in vials containing 250 µg (1.4×10^6 International Units [IU]/vial) sargramostim.

Lyophilized LEUKINE® is a sterile, white, preservative-free powder.

Each vial of lyophilized LEUKINE® also contains 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine, USP, as excipients. Biological potency is expressed in IU as tested against the WHO First International Reference Standard. The specific activity of LEUKINE® is approximately 5.6×10^6 IU/mg.

Storage and Stability

LEUKINE® should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Do not use beyond the expiration date printed on the vial.

Lyophilized LEUKINE® vials contain no antibacterial preservative, and therefore solutions should be administered as soon as possible.

6.3 Balstilimab (AGEN2034)

Description

Balstilimab is a human monoclonal antibody that targets PD-1. Engagement of PD-1 by its ligands, PD-L1 and PD-L2, leads to signal transduction that inhibits important aspects of T-cell function including proliferation, cytokine production and cytolytic activity. Balstilimab potently inhibits PD-1 binding to PD-L1 and PD-L2 and is intended to reverse the immunosuppressive effects of this signaling pathway in the context of tumor immuno-surveillance by T cells.

Form

Balstilimab has IgG4 heavy chains and immunoglobulin kappa light chains (IgG4κ). Balstilimab is produced using recombinant deoxyribonucleic acid technology in a Chinese hamster ovary mammalian expression system. The balstilimab drug product is provided as a sterile, single-use solution at 50 mg in a United States (US) Pharmacopeia compliant type 1 borosilicate 2 mL glass vial. The drug product is intended for dilution with 0.9% normal saline for IV administration.

Storage and Stability

The drug product vials should be stored at 2°C to 8°C (36°F to 46°F) and should be protected from light. A comprehensive stability program for the balstilimab drug product is in place to ensure product quality throughout the length of ongoing clinical investigations. Based on available stability data, balstilimab is stable for at least 36 months when stored according to conditions specified in the clinical supplies labeling.

Availability

Balstilimab is an investigational agent and will be supplied free-of-charge from VBI Vaccines Inc.

Preparation

Balstilimab drug product must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for preparation of dilutions and subsequent administration is provided in the Pharmacy Manual.

Balstilimab will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

Balstilimab drug product must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each trial center must be stored

carefully, safely, and separately from other drugs.

Once the vial is punctured, the balstilimab drug product must be diluted into appropriate volume of 0.9% sodium chloride (normal saline) solution in an infusion bag immediately. Infusion from the bag should be completed within 4 hours of vial puncture when the bag is stored at room temperature or within 24 hours when the bag is stored at 5°C±3°C (refrigerated conditions).

Any unused portion of solution should be discarded in biohazard waste disposal, with final disposal by accepted local and national standards of incineration.

Administration

Balstilimab will be administered by IV infusion every 2 weeks concurrent with VBI-1901. The first dose of balstilimab will be administered at Day 15, and then every 2 weeks until clinical disease progression (see master protocol section 11.2.3) or until no longer in the best interest of the participant, as described in section 3.2).

Balstilimab should be administered via IV infusion over 30 (± 15) minutes in the VBI-1901/balstilimab arm. Patients must be observed for 10 minutes post-balstilimab infusion for infusion-related reactions. Infusions will be followed immediately with a saline flush of the IV line, per institutional guidelines. In the VBI-1901/balstilimab arm, balstilimab should be administered first. However, the treating neurooncologist may opt to administer VBI-1901 first if desired for ease/convenience of the treating neurooncologist and the patient.

Ordering

VBI-1901 will be supplied by the sponsor as vials of final drug product (FDP) comprised of gB/pp65 eVLPs in an 8% sucrose solution with an opaque to milky appearance. It will be compounded at the hospital pharmacy with lyophilized GM-CSF (Leukine) supplied by the sponsor, as detailed in the Pharmacy Manual.
VBI-1901, GM-CSF, and Balstilimab will be ordered from each institution's individual pharmacy (or designee). The sponsor will work with the DFCI Coordinating Center once local IRB approval is received to ensure ample supplies of study agents are available at all approved sites.

Accountability

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

Destruction and Return

VBI-1901 and balstilimab will be destroyed on site according to institutional policies, documented in the Drug Accountability Record Form. At the time of expiration / study close, a drug disposition form provided by Drug Company Corporation will be sent out to be signed off by the Pharmacist and Investigator verifying the destruction of drug. At the end of the study, unused supplies of VBI-1901 and balstilimab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record For

7. STUDY CALENDAR

Assessment	Screen-ing[a]	D1[b]	Day 8 *(±1 Day)*	Day 15 *(±3 days)*	Day 29 *(±3 days)*	Day 43 *(±3 days)*	Day 57 *(±3 days)*	Adjuvant Cycles Day 1[z] *(±3 days)*	Adjuvant Cycles Day 15 *(±3 days)*	End of Tx[c]	30-Day Post Drug[d]	Active Follow-Up[e]	Long Term Follow-Up[f]
			Phone Call										
Informed Consent[g]	X												
Medical History[h]	X			X	X	X	X	X	X	X			
Inclusion/Exclusion Criteria[i]	X												
Vital signs[j]	X	X		X	X	X	X	X	X	X			
Physical Exam	X	X		X	X	X	X	X	X	X			
Neurologic Exam	X	X		X	X	X	X	X	X	X			
Karnofsky Performance Status[k]	X	X		X	X	X	X	X	X	X			
Pregnancy Test (β-HCG)[l]	X	X		X	X	X	X	X		X			
Coagulation[m]	X												
Hematology[n]	X	X		X	X	X	X	X	X	X			
8-hour Fasting Serum Chemistry[o]	X	X		X	X	X	X	X	X	X			
HbA1c		X		X						X			
Adverse Events[p]		X	X	X	X	X	X	X	X	X	X		
Concomitant Medications[q]	X	X	X	X	X	X	X	X	X	X	X		
Imaging – MRI[r]	X							X		X		X	
Response Assessment[s]								X		X		X	
Radiation[t]		----------X----------											
VBI-1901 Injection[u, v]		X			X		X	X					
Balstilimab Infusion[v, x]				X	X	X	X	X	X				
HCMV viremia[y]		X							X				
Serology (HIV, HCV,		X											

HBV)													
Reactogenicity[ee]				X	X	X							
Post-treatment therapies[cc]												X	X
Survival[dd]												X	X
GBM Biomarkers[aa]		X											
Anti-HCMV gB IgG ELISA assay								X[bb]					
HCMV IFN-γ ELISPOT assay								X[bb]					
FT3, FT4 & TSH			X					X					

a. All screening procedures to be performed within 28 days of initial registration unless otherwise specified. NOTE: refer to section 10 of master protocol for comprehensive details on screening assessments, initial registration, randomization assignment and second registration timing.

b. Day 1 assessments must be performed within 3 days of starting study treatment. Screening assessments may be utilized as baseline/Day 1 assessments if they fall within window.

c. End of Treatment: assessments to be performed within 7 days after last drug administration or within 7 days after decision to end treatment.

d. 30-Day Post Drug: a contact/visit is to be performed 30 days (+7 days) after date of last dose of drug taken on study. This may be performed via documented phone conversation with a study nurse or clinician or a clinic visit. All participants will be followed until resolution or stabilization of any serious or reportable adverse events occurring during treatment or starting within 30 days of last drug.

e. Active Follow-Up: participants who discontinue study treatment for reasons other than disease progression will be followed every 4 weeks (+/-1 week) via contact or medical record review and study team must continue monitoring participant's disease status by radiologic imaging at 8-week intervals (+/- 1 week) until (1) documented disease progression, (2), death, (3) participant withdraws from follow-up, or (4) end of study, whichever occurs first.

f. Long Term Follow-Up: participants will be followed every 8 weeks (+/-1 week) via contact or medical record review until death. Participants must be followed for survival data at every long-term follow-up time point and for post-treatment therapies and reason for stopping those therapies when available.

g. Informed Consent: must be obtained by MD attending. No study specific screening procedures may occur until after the initial informed consent process is completed. Initial informed consent may be obtained within 28 days of initial registration. Following initial registration and receipt of INSIGhT randomization assignment, participants must be sign the consent form specific to the assigned treatment arm prior to initiating treatment for that study arm.

h. Medical History: to include review of treatment history for GBM, any ongoing medical conditions & medical history pertaining to eligibility on study and involvement during study.

i. Inclusion/exclusion criteria: source documentation providing investigator's confirmation that the participant had met all master protocol eligibility criteria must be available prior to initial registration. See section 3 of master protocol for eligibility requirements for initial registration. See section 2 of this appendix for arm specific eligibility criteria.

j. Vital Signs: weight, heart rate, blood pressure, respiration rate, temperature. Vital signs must be performed prior to administration of treatment on treatment days. Height required only at screening.

k. Karnofsky Performance Status (KPS): see appendix A of master protocol.

l. Pregnancy Test: required for women of child bearing potential (see section 3 of master protocol for definition of women of child bearing potential). Pregnancy test can be either blood or urine sample.

m. Coagulation: PT/INR, PT, PTT required at screening only.

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

o. 8-hour Fasting Serum Chemistry: albumin, alkaline phosphatase (ALP), BUN, calcium, creatinine, glucose, potassium, SGOT (AST), SGPT (ALT), sodium, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed), amylase, lipase, and magnesium.

p. Adverse Events: adverse events experienced by participants will be collected and recorded from the first dose of treatment on-study up to the 30-Day Post Drug Visit of the last dose of study medication (+ 7 days depending on when 30-Day Post Drug visit/contact occurs).

q. Concomitant Medications: concomitant medications & reason for administration should be documented in the case history from date of consent up

to the 30-Day Post Drug Visit.

r. Imaging: gadolinium-enhanced contrast and non-contrast MRI. Initial imaging should be performed within 21 days prior to beginning study treatment. When feasible at site, Appendix D Recommended MRI Acquisition Protocol should be adhered to and the same imaging technique should be used on a participant throughout the trial. Local reading (investigator assessment) will be used to determine eligibility and for participant management. Adjuvant C1D1 imaging should be performed within 7 days prior to starting adjuvant treatment; subsequent imaging should be performed within 7 days prior to Day 1 of odd cycles (i.e every 8 weeks).

s. Response Assessment: Per RANO criteria (see section 11 of master protocol). Tumor response is assessed after every MRI (MRIs are performed at D1 of odd cycles)

t. Radiation: Refer to section 3.1 of this sub-study appendix for definition of standard radiation therapy per protocol.

u. VBI-1901+GM-CSF intradermal injections are to be administered once every 4 weeks (28 days ± 3 days) (section 3.2) beginning on Day 1 of radiation therapy. In the VBI 1901/balstilimab arm, balstilimab should be administered first. However, the treating neurooncologist may opt to administer VBI 1901 first if desired for ease/convenience of the treating neurooncologist and the patient.

v. Dose may be cancelled in the following cases: (1) confirmation of tumor progression on the most recent MRI. (2) withdrawal of study treatment for unacceptable toxicity or for another reason such as withdrawal of consent. Schedule the end of study visit for approximately 35 days after the last study dose was received.

x. Balstilimab intravenous infusion is to be administered every 14 days (± 3 days) (section 3.3). The first dose of balstilimab will be administered at Day 15.

y. HCMV viremia can be within 28 days.

z. 4 weeks +/- 3 days after radiation therapy completion patients will have restaging MRI and begin adjuvant cycles of treatment with VBI-1901+GM-CSF intradermal injections and balstilimab on Day 1 ± 3 days, and balstilimab alone on day 15 ± 3 days of every adjuvant cycle.

aa. MGMT promoter status, EGFR, EGFRvIII, PTEN, and p53 obtained from participant's medical records- Isocitrate dehydrogenase (IDH1/2) enzymes will be assessed on tumor specimen.

bb. Immunogenicity assessments to be completed every 3 cycles starting at adjuvant C2D1 (e.g., cycles 2, 5, 8, 11, 14, and 17). Immunogenicity assessment to occur on treatment visits where VBI-1901 and balstilimab are both administered.

cc. Post-treatment Therapies: start/stop dates, names of treatment regimens and reason for stopping should be collected when available.

dd. Survival: date of death and reason must be collected for overall survival purposes.

ee. Reactions to vaccine will be assessed 30 minutes following each immunization and during the 28 following days.

8. MEASUREMENT OF EFFECT

Refer to section 11 of master INSIGhT protocol for details on measurement of effect.

9. GRADING OF LOCAL REACTIONS

Table 1: Grading of Local Reactions

	Grade 1	Grade 2	Grade 3	Grade 4
Pain (pain without touching)	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness (pain when area is touched)	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Pruritus associated with injection See also Skin: Pruritus (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

10. REFERENCES

1. Roy P, Noad R. Virus-like particles as a vaccine delivery system: myths and facts. Human vaccines 2008;4:5-12.

2. Tan M, Jiang X. Subviral Particle as Vaccine and Vaccine Platform. Current opinion in virology 2014;0:24-33.
3. Green N, Shinnick TM, Witte O, Ponticelli A, Sutcliffe JG, Lerner RA. Sequence-specific antibodies show that maturation of Moloney leukemia virus envelope polyprotein involves removal of a COOH-terminal peptide. Proceedings of the National Academy of Sciences of the United States of America 1981;78:6023-7.
4. Patnaik A, Chau V, Wills JW. Ubiquitin is part of the retrovirus budding machinery. Proceedings of the National Academy of Sciences of the United States of America 2000;97:13069-74.
5. Strack B, Calistri A, Accola MA, Palù G, Göttlinger HG. A role for ubiquitin ligase recruitment in retrovirus release. Proceedings of the National Academy of Sciences of the United States of America 2000;97:13063-8.
6. Shields A, Witte ON, Rothenberg E, Baltimore D. High frequency of aberrant expression of moloney murine leukemia virus in clonal infections. Cell;14:601-9.
7. Sherer NM, Lehmann MJ, Jimenez-Soto LF, et al. Visualization of Retroviral Replication in Living Cells Reveals Budding into Multivesicular Bodies. Traffic 2003;4:785-801.
8. Cobbs C, Khan S, Matlaf L, et al. HCMV glycoprotein B is expressed in primary glioblastomas and enhances growth and invasiveness via PDGFR-alpha activation. Oncotarget 2014;5:1091-100.
9. Mitchell DA, Batich KA, Gunn MD, et al. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma participants. Nature 2015;519:366-9.
10. Galon J, Costes A, Sanchez-Cabo F, et al. Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome. Science 2006;313:1960-4.
11. Tomtishen Iii JP. Human cytomegalovirus tegument proteins (pp65, pp71, pp150, pp28). Virology Journal 2012;9:22-.
12. Plotkin S. The history of vaccination against cytomegalovirus. Med Microbiol Immunol 2015;204:247-54.
13. Kirchmeier M, Fluckiger AC, Soare C, et al. Enveloped Virus-Like Particle Expression of Human Cytomegalovirus Glycoprotein B Antigen Induces Antibodies with Potent and Broad Neutralizing Activity. Clinical and Vaccine Immunology: CVI 2014;21:174-80.
14. Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve participant outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014;20:295-308.
15. Dranoff G, Jaffee E, Lazenby A, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proceedings of the National Academy of Sciences of the United States of America 1993;90:3539-43.
16. Arellano M, Lonial S. Clinical uses of GM-CSF, a critical appraisal and update. Biologics 2008;2:13-27.
17. .Clive KS, Tyler JA, Clifton GT, et al. Use of GM-CSF as an adjuvant with cancer vaccines: beneficial or detrimental? Expert Review of Vaccines 2010;9:519-25.
18. Schijns VEJC, Pretto C, Devillers L, et al. First clinical results of a personalized immunotherapeutic vaccine against recurrent, incompletely resected, treatment-resistant glioblastoma multiforme (GBM) tumors, based on combined allo-and auto-immune tumor reactivity. Vaccine 2015; 33(23): 2690-6.
19. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
20. Frazier et al., 2015

21. Ponce R, Abad L, Amaravadi L, et al. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. Regul Toxicol Pharmacol 2009;54:164-82.
22. Rojko JL, Evans MG, Price SA, et al. Formation, clearance, deposition, pathogenicity, and identification of biopharmaceutical-related immune complexes: review and case studies. Toxicol Pathol 2014;42:725-64.
23. Sammons LS, Kenyon RH, Pedersen CE, Jr. Effect of vaccination schedule on immune response of Macaca mulatta to cell culture-grown Rocky Mountain spotted fever vaccine. J Clin Microbiol 1976;4:253-7.
24. Sester M, Sester U, Gartner B, et al. Sustained high frequencies of specific CD4 T cells restricted to a single persistent virus. J Virol 2002;76:3748-55.
25. Pauken KE, Torchia JA, Chaudhri A, et al. Emerging concepts in PD-1 checkpoint biology. Semin Immunol 2021;52:101480.
26. O'Malley DM, Neffa M, Monk BJ, et al. Dual PD-1 and CTLA-4 checkpoint blockade using balstilimab and zalifrelimab combination as second-line treatment for advanced cervical cancer: an open-label Phase II study. J Clin Oncol 2021;JCO2102067.
27. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016;13:473-86.
28. Kumar V, Chaudhary N, Garg M, et al. Current Diagnosis and Management of Immune Related Adverse Events (irAEs) Induced by Immune Checkpoint Inhibitor Therapy. Front Pharmacol 2017;8:49.
29. Brennan FR, Dougan G. Non-clinical safety evaluation of novel vaccines and adjuvants: new products, new strategies. Vaccine 2005;23:3210-22.
30. Tavares Da Silva F, De Keyser F, Lambert PH, et al. Optimal approaches to data collection and analysis of potential immune mediated disorders in clinical trials of new vaccines. Vaccine 2013;31:1870-6.
31. Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28:4531-8.

DFCI REPORTABLE AE COVERSHEET – INSIGhT VBI-1901/Balstilimab (AGEN2034) ARM

DF/HCC Protocol No. 16-443 **Drug Company Tracking No.** VBI-1901/AGEN2034-

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this AE):

☐ Dr. Patrick Y. Wen and Dana-Farber Coordinating Center
Email: NeuroOnc_SAE@dfci.harvard.edu

☐ VBI Vaccines Fax: 908-673-9115 ☐Email: vbi1901INSIGhTsae@vbivaccines.com

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

Participant # and Initials:
Date Event Met Reporting Criteria (as defined in protocol):
Type of Report: ☐Initial ☐Follow-up

CTCAE Event #1 Description:	CTCAE Event #2 Description (if applicable): *NOTE: use another coversheet if more than 2 events are being reported at this time*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5/death
Expectedness with **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A	Expectedness with **Radiation Therapy**: ☐Expected ☐Unexpected ☐ N/A
Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Radiation Therapy**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness with **VBI-1901:** ☐Expected ☐Unexpected ☐ N/A	Expectedness with **VBI-1901:** ☐Expected ☐Unexpected ☐ N/A
Attribution to **VBI-1901:** ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **VBI-1901:** ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Expectedness with **Balstilimab (AGEN2034)** ☐Expected ☐Unexpected ☐ N/A	Expectedness with **Balstilimab (AGEN2034)** ☐Expected ☐Unexpected ☐ N/A
Attribution to **Balstilimab (AGEN2034)** ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A	Attribution to **Balstilimab (AGEN2034)** ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite ☐ N/A
Reporting Investigator (print):	

Signature of Reporting Investigator: _____ Date:_____