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Drug Distribution and Pharmacodynamic Study of Pulsatile Lapatinib in Surgically Accessible EGFR-Amplified Recurrent High-Grade Glioma

A Protocol of the Adult Brain Tumor Consortium (ABTC)

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1.0 OBJECTIVES

Primary Objectives

Group A:

1. To achieve an intratumoral lapatinib concentration of at least 1.5 μM in at least 70% of patients 3 hours after the last dose of pulsatile lapatinib.

Group A and Reference Group:

2. To determine the pharmacodynamic (PD) effect of pulsatile lapatinib (at pulsatile MTD) on EGFR phosphorylation (using Mesoscale Discovery ELISA assay for total and phospho-EGFR). The successful PD effect is defined by EGFR blockade if at least 70% of the patients have an 80% reduction of EGFR phosphorylation/total in Group A tumors compared to the Reference Group tumors.

Secondary/Exploratory Objectives:

Group A and Reference Group:

1. To evaluate the safety profile of pulsatile lapatinib in pre-operative patients with EGFR amplified recurrent high-grade glioma; to evaluate acute and late toxicities associated with pulsatile lapatinib

2. To determine the effect of lapatinib on tumor cell proliferation (KI-67 staining) (Group A compared to Reference Group)

3. To determine the ex-vivo sensitivity of tumor sphere cultures to lapatinib

4. To assess tumor objective response rate (ORR)

5. To estimate overall survival (OS)

6. To estimate progression-free survival

2.0 BACKGROUND AND RATIONALE

2.1 Study Disease

High-Grade Glioma

Glioblastoma (WHO grade IV) and anaplastic glioma (WHO grade III) represent the most common malignant brain tumor in adults. These tumors are universally fatal with most patients succumbing to their disease within ten years, and there is a dire need for the development of novel therapeutics (Wen 2008). Inhibitors of deregulated signaling pathways are active agents in a variety of human cancers (Sawyers 2009, Sellers 2011) and represent a compelling area of drug development for high-grade glioma because many of these tumors harbor genetic alterations in growth factor-signaling pathways (Killela et al. 2013, Parsons et al. 2008).

2.2 Lapatinib

Lapatinib (Tykerb) is a dual EGFR/erbB2 kinase inhibitor. It is currently approved for the treatment of patients with advanced breast cancer in combination with capecitabine. Its activity against EGFR has led to two trials exploring the use of lapatinib in recurrent glioblastoma (GBM).

Lapatinib in clinical studies

As of 05-Dec-2011, a total of 10 Phase I studies in healthy volunteers, 29 Phase I studies in subjects with cancer, and 55 Phase II or Phase III clinical efficacy studies in subjects with cancer have been completed or are active in the GlaxoSmithKline (GSK)-sponsored lapatinib program. For this investigator's brochure (IB), the definition of the term "completed" refers to a study for which a final (End of Study) clinical report is available.

All studies with subjects still on treatment are considered active. Once a study has met protocol-defined events or objectives, an analysis is usually performed; however, subjects may continue to receive study medication during or after the completion of this analysis. These subjects are followed per protocol, and a final safety analysis is performed once all subjects have withdrawn from study medication.

A total of 385 healthy volunteers and over 1,100 subjects with cancer have been enrolled in Phase I studies. Over 30,000 subjects have been enrolled in Phase II, III and IV clinical monotherapy and combination therapy studies, of which over 27,000 subjects have been enrolled in breast cancer studies. Other subjects were enrolled in studies evaluating the use of lapatinib in the treatment of bladder, colorectal, head and neck, lung, renal, cervical, gastric, ovarian, and uterine cancer, relapsed adenocarcinoma of the esophagus, including tumors of the gastroesophageal junction and gastric cardia, and in the treatment of malignant gliomas.

Summary of lapatinib safety

As of 05-Dec-2011 565 subjects have died due to events reported as serious adverse events (SAEs). One hundred and eleven of these deaths were assessed as related to investigational product (IP) by the investigator; 87 subjects received lapatinib, 13 subjects received comparator, 10 subjects received placebo and 1 subject remained blinded. Based on current exposure, the estimated incidence rate of fatal outcomes related to lapatinib was 0.4% (87/20,586), compared with a rate of 0.3% (23/7421) for subjects who received placebo or comparator. Twenty-one of the lapatinib subjects received lapatinib monotherapy, the remaining 66 received lapatinib in combination with other chemotherapy (including capecitabine, paclitaxel, pazopanib, and trastuzumab). The reported fatal events were all expected events for the cancer treatment regimens and/or the population under study.

The most common adverse events (AEs) in clinical studies, regardless of relationship to study drug, were diarrhea, rash, and nausea. Majority of these AEs were of Grade 1 or 2 severity, and resolved. These events are included in the core safety information (CSI) for lapatinib and are consistent with the safety profile of lapatinib as reported for the program as a whole.

Lapatinib dosed at 750mg twice a day was used in a similar study to this with neoadjuvant delivery followed by craniotomy and tissue removal (NABTC 04-01). There were no safety signals identified associated with wound healing or wound infections. There is no identified experience using pulsatile lapatinib in the setting of any surgery including craniotomy. The safety concerns associated with wound healing or wound infection are unknown with the doses provided with this study.

Summary of clinical pharmacology studies

In healthy volunteer Phase I studies, most AEs reported were considered Grade 1 in severity and resolved spontaneously. Overall, the most frequently reported AEs were Grade 1 headache, GI-related events (diarrhea, loose stools, dyspepsia, gas, flatulence), and rash. There were no deaths or SAEs reported in the healthy volunteer studies while subjects were on study. There were no consistent lapatinib-related changes in physical examinations, hematology or clinical chemistry values, electrocardiogram (ECG), urinalyses, or ophthalmologic examinations.

Of the over 1,100 subjects with cancer enrolled in Phase I lapatinib studies by 05-Dec-2011, 357 subjects had received single-agent lapatinib in eight Phase I studies and over 600 subjects had received lapatinib in combination with other agents including chemotherapeutic or hormonal anticancer treatments in 20 Phase I studies including one Phase I component of a Phase I/Phase II study and two Phase I continuation (rollover) studies. In the monotherapy lapatinib studies, lapatinib was administered at dosages ranging from 175 mg to 1800 mg once daily or 500 mg to 900 mg BID. In the lapatinib-

based combination studies, lapatinib was administered at dosages ranging from 500 mg to 1500 mg once daily.

In completed lapatinib Phase I monotherapy studies in subjects with cancer, most AEs reported were Grade 1 or 2 in severity with the most frequently reported AEs being diarrhea, rash, nausea, anorexia, and fatigue. There were no consistent lapatinib-related changes in physical examinations, hematology or clinical chemistry values, ECG, urinalyses, or ophthalmologic examinations.

Summary of clinical efficacy studies: lapatinib monotherapy

As of the clinical data cut-off date of 05-Dec-2011, over 5,000 subjects have been enrolled in 12 completed and 4 active Phase II or III lapatinib monotherapy studies. In the monotherapy studies, lapatinib was administered at dosages ranging from 1000 mg once daily to 1500 mg once daily or from 500 mg BID to 750 mg BID. Results from the data analyses performed for 15 lapatinib monotherapy studies suggest that lapatinib was generally well tolerated in subjects with cancer. The most common AEs regardless of relationship to drug were diarrhea, rash, and nausea. The majority of these AEs were of Grade 1 or Grade 2 severity. These events are included in the CSI for lapatinib and are consistent with the safety profile of lapatinib as reported for the program as a whole.

Efficacy data from the 15 monotherapy studies with data analyses are summarized in Section 5.3.4.1 of the lapatinib Investigator's Brochure.

2.3 Rationale

The epidermal growth factor receptor (EGFR) is a member of the EGFR family of receptor tyrosine kinases, which also includes HER2 (ErbB2), HER3 (ErbB3), and HER4 [ErbB4 (Yarden et al. 2001). EGFR has generated particular interest as a drug target in GBM because of the high frequency of EGFR alterations in this disease (Furnari et al. 2007) and because ATP-site competitive EGFR kinase inhibitors are active agents in patients with EGFR mutant lung cancer (Pao 2010). EGFR kinase inhibitors that received regulatory approval for the treatment of lung cancer (erlotinib, gefitinib), however, have shown disappointing results in patients with GBM (Brandes 2008). Reasons for this lack of response in GBM remain poorly understood and may include redundancy in signaling pathways (Stommel 2007) and intratumoral heterogeneity (Inda 2010).

One key difference between EGFR in GBM and lung cancer is the distribution of mutations within the EGFR coding sequence. EGFR mutations in lung cancer reside in the intracellular kinase domain (Sharma SV 2007). EGFR mutations in GBM cluster in the extracellular (EC) domain and include in-frame deletions (such as the common "variant III" [Furnari et al. 2007]) and missense mutations (Lee et al. 2006). In contrast to the most common EGFR kinase domain mutants in lung cancer which respond well to the first-generation EGFR kinase inhibitors erlotinib and gefitinib, we recently found that the most common oncogenic EGFR alterations in GBM are relatively insensitive to erlotinib

(Vivanco et al. 2012). Instead, these mutants are preferentially inhibited by EGFR inhibitors that can only be accommodated by the inactive conformation of the EGFR catalytic pocket as the result of their bulky aniline substituents (lapatinib, HKI-272 [Wood et al. 2004, Eck et al. 2010]). These results from Vivanco et al. are consistent with structural data (Park and Lemmon 2012) and argue for focused clinical development of type II EGFR kinase inhibitors such as lapatinib for EGFR-mutant GBM.

A number of recent studies have shown that the level of kinase inhibition is a critical determinant of the biological effects of kinase inhibitors on cancer cells expressing oncogenic kinases. First, near complete inhibition of BCR-ABL, even for only minutes, irreversibly committed *BCR-ABL* mutant leukemia cells to cell death (Shah et al. 2008). Second, greater than 80% inhibition of ERK phosphorylation in the tumors of patients correlated with clinical response in *BRAF* mutant melanoma (Bollag et al. 2010). Third, intermittent, high-dose lapatinib was more effective than daily, lower dose lapatinib in xenograft models of two different *ERB*-driven cancers, namely *HER2* amplified BT474 breast cancer xenografts (Amin et al. 2010) and *EGFR* amplified GS676 glioblastoma xenografts (Vivanco et al. 2012). Titration experiments with multiple EGFR-shRNAs genetically confirmed the requirement of near complete EGFR inhibition for induction of cell death in EGFR mutant glioblastoma cells (Vivanco et al. 2012). Of note, we also found that near complete EGFR inhibition is able to overcome the effects of PTEN loss on EGFR kinase inhibitor resistance (Vivanco et al. 2010) and to induce cell death in EGFR mutant glioblastoma cells with endogenous loss of PTEN (Vivanco et al. 2012).

A critical aspect of potent EGFR blockade is the "therapeutic window" of this strategy. While EGFR knockdown and lapatinib robustly induced death and blocked colony formation in GBM cells with EGFR gene amplification or EGFR mutation (Vivanco et al. 2012), reflecting their "dependence" on EGFR signals for survival, neither EGFR knockdown nor pharmacological EGFR blockade induced cell death in immortalized human astrocytes or in GBM cells that were wildtype for EGFR. Furthermore, clinical studies at Memorial Sloan Kettering Cancer Center have shown that high-dose intermittent dosing of the type I EGFR kinase inhibitor erlotinib (weekly administration of 1200-2000 mg) is well tolerated (Milton 2006, Clarke et al. 2010, Grommes et al. 2011).

Unfortunately, current dosing schedules of lapatinib do not reach sufficiently high intratumoral drug concentrations to potently inhibit EGFR in GBM. When given at a dose of 750 mg twice daily (NABTC 04-01 in Vivanco et al. 2012), lapatinib only inhibited EGFR by about 50 % (based on ratio of phosphorylated to total EGFR using the MSD mesoscale assay [Vivanco et al. 2012]) and failed to prolong progression-free survival in patients with recurrent GBM in that study, and another recent phase I/II trial (Thiessen et al. 2010). Unfortunately, these trials did not restrict patient enrollment to EGFR-mutant GBMs. In the NABTC 04-01 study, for example, neither of the two GBM patients with intratumoral lapatinib concentrations shown to induce cell death in-vitro (>1,500 nM) and EGFR protein overexpression could be evaluated for therapeutic response.

The current trial restricts enrollment to patients with EGFR amplified high grade glioma because glioma cells with amplification of wildtype EGFR gene are more sensitive to lapatinib than cells with non-amplified wildtype EGFR (Vivanco et al. 2012). Furthermore,

the EGFR VIII mutation in GBM occurs almost exclusively in the setting of EGFR gene amplification and EGFRvIII showed greater sensitivity to type II EGFR kinase inhibitors (such as lapatinib) than to the type I EGFR kinase inhibitor erlotinib.

The pharmacokinetic (PK) goal of this study is to achieve intratumoral concentrations of lapatinib >1,500 nM. The pharmacodynamic (PD) goal is to achieve near complete inhibition of pEGFR, defined as 80% reduction of EGFR phosphorylation. Of note, the feasibility of such "pulsatile" lapatinib therapy has already been explored in advanced solid tumors and found to be well tolerated (Chien et al. 2009).

2.4 Correlative Studies Background

EGFR gene amplification in tumor cells (Integral): EGFR mutations in high-grade glioma include point mutations and a variety of structural alterations (Frederick et al. 2000, Frattini et al. 2013, Brennan et al. 2013, Ciriello et al. 2013). Since these mutations are commonly accompanied by amplification of the EGFR gene, evidence of regional DNA amplification of EGFR will be used as an integral biomarker. EGFR amplification will be determined centrally by fluorescence in-situ hybridization (FISH) (See Section 9.5.2).

Tumor lapatinib concentrations (Integrated): See Section 2.3, above, regarding the rationale and selection of pharmacokinetic endpoints. The concentration of lapatinib in tumor samples will be determined using a validated LC-MS/MS assay. Details of the sample collection, processing, storage and shipment procedures are provided in Section 9.5.5.

EGFR phosphorylation in tumor cells (Integrated): See Section 2.3, above, regarding the rationale and selection of pharmacodynamic endpoints. EGFR phosphorylation will be determined with the mesoscale electroluminescence platform which has shown greater sensitivity than other ELISA-based assays (Sharma J et al. 2012) and is widely used in the evaluation of signal transduction inhibitors (http://www.mesoscale.com). Details of the procedures for sample collection, sample batching, and assay performance characteristics are provided in Section 9.5.4., Section 9.5.6, and Appendix IV.

Plasma lapatinib concentrations (Exploratory): The concentration of lapatinib in plasma samples will be determined using a validated LC-MS/MS assay. Details of the PK sample collection, processing, storage and shipment procedures are provided in Section 9.5.3.

Tumor cell proliferation (KI-67 staining) (Exploratory): We will compare tumor cell proliferation in lapatinib-treated patients (group A) with tumor cell proliferation in lapatinib-naïve patients (reference group). We will also examine tumor cell proliferation in the archival sample from both groups of patients and compare it to the matched specimen from the current protocol surgery (matched pair comparison). Together, these

analyses aim to determine the effect of lapatinib on tumor cell proliferation. Details of the procedures for sample collection and staining are provided in Section 9.5.2.

Ex-vivo sensitivity of tumor sphere cultures to lapatinib (Exploratory): Compared to commercially available human glioblastoma cell lines grown under standard tissue culture conditions, freshly derived tumor sphere cultures grown under serum-free conditions (with exogenous FGF/EGF) more closely resemble the original human tumor sample (Pandita et al. 2004, Lee J et al. 2006). We will therefore generate such cultures from all patients in the study (Group A and Reference Group) and examine their lapatinib sensitivity ex-vivo using a Trypan Blue exclusion Assay (Vivanco et al. 2012). Details of the sample collection and shipping procedures are provided in Section 9.5.7.

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Patient Sample

Sample Size:
Group A: 18 patients
Reference Group: 15 patients

Accrual Rate:
3 patients per month

Gender:
Male and female

Age:
Patients must be at least 18 years of age.

Race/Ethnicity:
Minorities will be actively recruited. No exclusion to this study will be based on race or ethnicity.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	2		+	2		=	4	
Not Hispanic or Latino	11		+	18		=	29	
Ethnic Category: Total of all subjects	13	(A1)	+	20	(B1)	=	33	(C1)
Racial Category								
American Indian or Alaskan Native	0		+	0		=	0	
Asian	2		+	2		=	4	
Black or African American	2		+	3		=	5	
Native Hawaiian or other Pacific Islander	0		+	0		=	0	
White	9		+	15		=	24	
Racial Category: Total of all subjects	13	(A2)	+	20	(B2)	=	33	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

3.2 Eligibility Criteria

1. Patients must have histologically proven WHO grade IV glioblastoma/ gliosarcoma or WHO grade III glioma (anaplastic astrocytoma, anaplastic oligodendroglioma, mixed anaplastic oligoastrocytoma, anaplastic ependymoma) which is progressive or recurrent following radiation therapy ± chemotherapy.

2. Patients must have measurable, supratentorial contrast-enhancing progressive or recurrent high-grade glioma by MRI imaging within 21 days of starting treatment. Patient must be able to tolerate MRIs.

3. Patients may have an unlimited number of prior therapy regimens.

4. Patients must have recovered from severe toxicity of prior therapy. The following intervals from previous treatments are required to be eligible:

    - 12 weeks from the completion of radiation
    - 6 weeks from a nitrosourea chemotherapy
    - 3 weeks from a non-nitrosourea chemotherapy
    - 4 weeks from any investigational (not FDA-approved) agents
    - 4 weeks from the last treatment with bevacizumab
    - 2 weeks from administration of a non-cytotoxic, FDA-approved agent other than bevacizumab (e.g., hydroxychloroquine, etc.)

5. Patients must be undergoing surgery that is clinically indicated as determined by their care providers. Patients must be eligible for surgical resection according to the following criteria:

    - Expectation that the surgeon is able to resect at least 500 mg of tumor from enhancing tumor and 100 mg from non-enhancing tumor with low risk of inducing neurological injury.

6. Patient tumor sample must have evidence of EGFR gene amplification by FISH performed using a CLIA-certified laboratory assay. See Section 9.5.2 for details.

7. Paraffin embedded tissue must be available from initial surgical resection at diagnosis (prior to any treatment).

8. Patients must be 18 years of age or older.

9. Patients must have a Karnofsky Performance Status ≥ 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).

10. Patients must have the following organ and marrow function:

Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥ 9 g/dL
Total bilirubin	≤ institutional upper limit of normal
AST (SGOT)/ALT (SGPT)	≤ 3 × institutional upper limit of normal
Creatinine	≤ institutional upper limit of normal

	OR
Creatinine clearance	≥60 ml/min/1.73m^2 for patients with creatinine levels above institutional normal
APTT/PTT	≤ 1.5 x institutional upper limit of normal

11. Patients must have left ventricular ejection fraction (LVEF) within normal institutional limits within 21 days of starting treatment.

12. Patients must have a 12-lead electrocardiogram performed within 2 weeks of treatment start with QTC ≤470 msec.

13. Patients must be able to provide written informed consent.

14. Women of childbearing potential must have a negative serum pregnancy test prior to study entry. Women of childbearing potential 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. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and for 4 months after completion of lapatinib administration.

15. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with prior malignancies must be disease-free for ≥ five years.

16. Patients must be able to swallow medication by mouth, either tablets or dispersed tablets in solution.

3.3 Ineligibility Criteria

1. Patients may not be receiving any other investigational agents.

2. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to lapatinib are ineligible. The lapatinib Investigator Brochure can be referenced for more information.

3. Patients with prior therapy with EGFR inhibitors are ineligible because treatment with EGFR kinase inhibitors or other EGFR-targeted agents has the potential to deplete the tumor of EGFR-amplified or EGFR mutant cell populations and confound the evaluation of lapatinib effects on EGFR phosphorylation. Patients with prior EGFRvIII vaccine are eligible if recurrent tumor is positive for EGFR gene amplification.

4. Patients on enzyme-inducing anti-epileptic drugs (EIAED) are not eligible for treatment on this protocol. Patients may be on non-enzyme inducing anti-epileptic drugs or not be taking any anti-epileptic drugs. Patients previously treated with EIAED may be enrolled if they have been off the EIAED for 10 days or more prior to the first dose of lapatinib.

5. Patients must not have evidence of significant hematologic, renal, or hepatic dysfunction.

6. Patients must not have evidence of significant intracranial hemorrhage.

7. Patients with uncontrolled intercurrent illness including, but not limited to, hypertension, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.

8. Pregnant women are excluded from this study because lapatinib has potential for teratogenic or abortifacients effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with lapatinib, breastfeeding should be discontinued if the mother is treated with lapatinib.

9. HIV-positive patients on strong CYP3A4 inducers or inhibitors are ineligible because of the potential for pharmacokinetic interactions with lapatinib.

10. Patients who have acute or currently active/requiring anti-viral therapy hepatic or biliary disease are ineligible (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases from the primary brain tumor, or stable chronic liver disease per investigator assessment).

11. Patients receiving P-gp inhibitors are ineligible. See Section 4.4 for a list of P-gp inhibitors.

12. Patients who are receiving a drug that has a risk of QTc prolongation if QTc is ≥ 460 msec. are ineligible.

4.0 TREATMENT PLAN

This study will assess whether oral pulsatile lapatinib dosing at the established MTD (2500mg BID, for two days) provides adequate intratumoral drug concentrations and EGFR inhibition for future studies that utilize 2 days on/5 days off regimen in EGFR-amplified high-grade glioma.

Extent of EGFR inhibition will be determined through comparison of EGFR phosphorylation in tumor tissue from patients receiving preoperative lapatinib (**Group A**) compared to a **Reference Group** of patients who do not receive preoperative lapatinib.

4.1 Treatment Schema

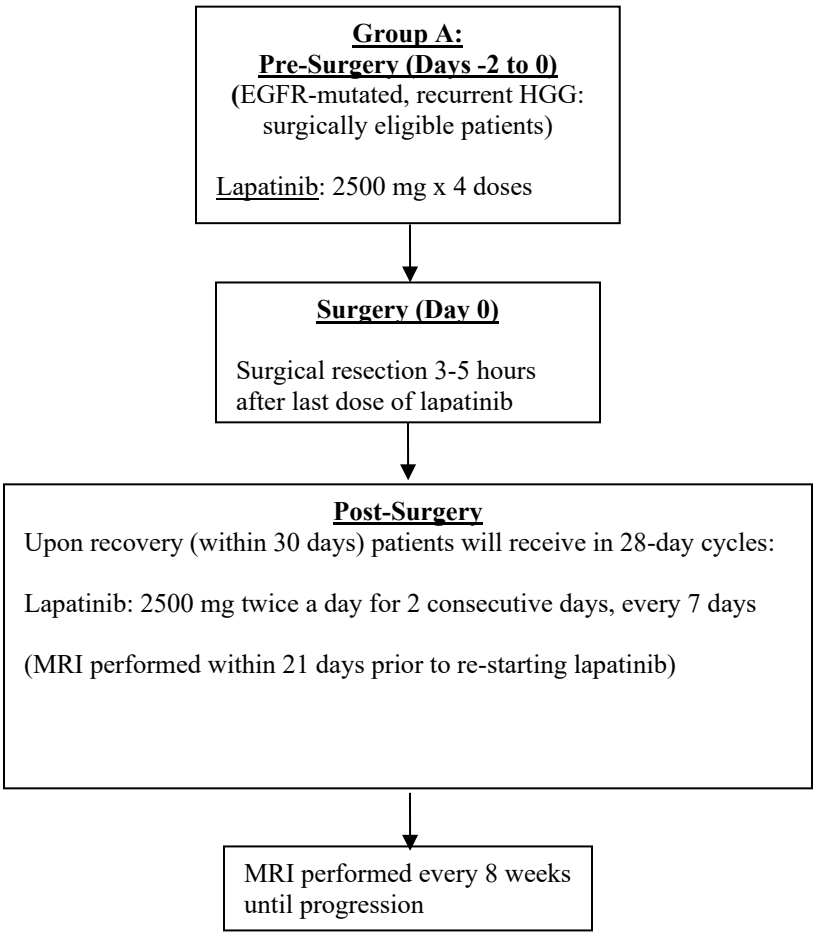
All patients must have recurrent EGFR-amplified high-grade glioma and be candidates for re-resection.

The first 8 patients on the study will be enrolled into Group A and receive lapatinib pre-operatively for 4 doses. Intratumoral drug levels will be analyzed following tissue sample collection during surgery. If adequate intratumoral drug concentration levels (1.5 μM or higher) are reached in at least 3 of the initial 8 patients, the study will proceed with further enrollment as follows. See Section 11.0, Primary Objectives and Sample Size for details.

After the initial 8 patients are enrolled, subsequent patients will be sequentially assigned to either receive lapatinib pre-operatively for 4 doses (Group A) or to receive no drug prior to surgical resection (Reference Group): 20 patients will alternate enrollment into either Group A or the Reference Group (10 additional patients into Group A to complete the group, and 10 patients into the Reference Group); then 5 additional patients will enroll into the Reference Group to complete the group. Fresh and paraffin embedded tissue from surgical resection will be utilized for correlative studies.

Group A

Patients with recurrent, EGFR-mutated high-grade glioma who require surgical resection will receive a pre-operative course of lapatinib at a dose of 2500mg BID for four doses prior to scheduled surgical resection for recurrent high-grade glioma. Patients may take one extra dose for a total of 5 doses if unexpected logistical problems delay the surgery. Patients will take the last dose of lapatinib ideally 3-5 hours before surgery to resect the tumor. Tumor tissue will be snap-frozen for determination of EGFR phosphorylation and intratumoral drug concentration. Plasma samples will be collected at selected time points to determine plasma levels of lapatinib during surgery.



Group A Treatment Plan

Patients should begin presurgical treatment with lapatinib starting 2 days (Day -2) prior to the day of scheduled tumor resection (Day 0). Doses of lapatinib should be taken 12 hours apart ± 2 hours. The first dose should be taken in the evening on Day -2, the second dose should be taken in the morning on Day -1, the third dose should be taken in the evening on Day -1, and the fourth dose should be taken on the morning of surgery. One additional dose is permitted 12 hours after the fourth dose ± 2 hours if unexpected logistical problems delay the surgery.

Patients who do not receive at least 4 doses of lapatinib prior to surgery will be replaced in the cohort; tissue from protocol surgery will no longer be required for these patients

but they may continue with post-surgical treatment provided any toxicity from pre-surgical dosing resolves within protocol parameters.

In order to accommodate biological sample collection and shipping, **surgery must take place Monday-Thursday**, with the exception of patients being treated at Memorial Sloan-Kettering Cancer Center: these patients may undergo surgery Monday- Friday (since tumor samples will be processed at MSKCC, these samples will not require overnight shipping).

Surgery, during which tumor tissue samples will be acquired, should be performed ideally within 3 to 5 hours after taking the last dose of lapatinib. The time that the last dose is taken on the day of tumor resection must be recorded. Patients whose last dose of lapatinib is greater than 12 hours prior to surgery (the time tumor tissue is removed) will be replaced in the cohort; tissue from protocol surgery will no longer be required for these patients but they may continue with post-surgical treatment provided any toxicity from pre-surgical dosing resolves within protocol parameters.

Research blood samples will be collected at baseline prior to the first presurgical dose and shortly before and after the time of surgery for determining the concentration of lapatinib in plasma. See Section 9.5.3 for details.

Tumor specimens will be analyzed for drug levels and a portion will be snap frozen for determination of EGFR phosphorylation. Instructions for collecting and handling tumor specimens are in Sections 9.5.1, 9.5.4, and 9.5.5.

Following surgery, patients will continue with standard post-operative management.

After recovery from surgical resection, patients will receive lapatinib post-operatively twice a day for two consecutive days every 7 days (2 days on/5 days off) in 28-day cycles.

Adequate recovery from surgical resection includes, but is not limited to, the following:

- No signs or symptoms of infections related to the surgical wound (*i.e.*, increasing erythema or cellulitis of the surrounding area, large amount of drainage, fever)
- Wound edges have healed

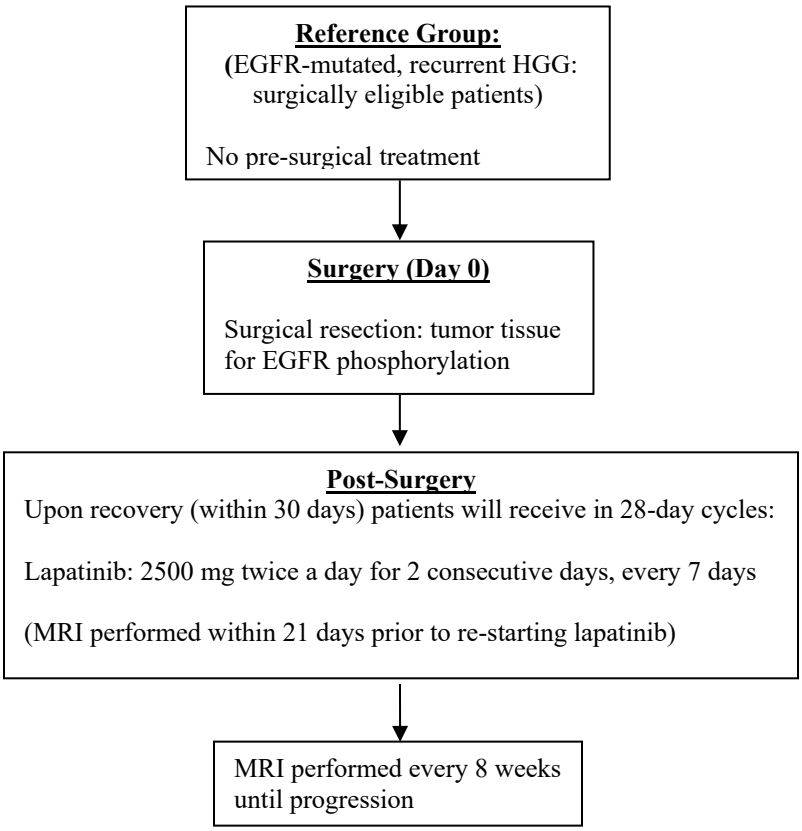
Post-operatively, patients must begin treatment within 30 days of surgical resection, and preferably within 3 weeks of the post-operative MRI; if more than 3 weeks elapse after the post-operative MRI, the patient will need a new MRI.

Patients will be followed by routine blood work, general and neurological examination, and MR imaging. See Section 9.1 for schedule.

Patients may continue to receive cycles of lapatinib until tumor progression, development of unacceptable toxicity, or meeting other criteria for going off treatment (Section 10.1). Patients will be followed for adverse events for at least 30 days after the last dose of lapatinib. All patients will be followed for survival.

Reference Group

Patients with recurrent, EGFR-amplified high-grade glioma who require surgical resection will go to surgery to resect brain tumor. A portion of tumor tissue will be snap-frozen for determination of EGFR phosphorylation.



Reference Group Treatment Plan

Patients in this group will receive no study medication pre-surgically.

In order to accommodate biological sample collection, **surgery must take place Monday-Thursday**, with the exception of patients being treated at Memorial Sloan-Kettering Cancer Center: these patients may undergo surgery Monday- Friday.

Tumor tissue samples will be acquired during surgery to resect brain tumor. Tumor specimens will be snap frozen for determination of EGFR phosphorylation. Instructions for collecting and handling tumor specimens are in Sections 9.5.1 and 9.5.4.

Following surgery, patients will continue with standard post-operative management.

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Patients may continue to receive cycles of lapatinib until tumor progression, development of unacceptable toxicity, or meeting other criteria for going off treatment (Section 10.1). Patients will be followed for adverse events for at least 30 days after the last dose of lapatinib. All patients will be followed for survival.

4.2 Treatment Requirements

All eligible patients who consent to this study must have a baseline pre-treatment MRI within 21 days prior to the initiation of treatment, and a post-surgical MRI within 21 days prior to starting Cycle 1.

Prior to every cycle patients must have:

1) ANC ≥ 1500/µl and platelets ≥ 100,000 /µl.
AND
2) All toxicities recovered to ≤ grade 1 or ≤ baseline

4.3 Drug Administration

Lapatinib treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be provided with a medication diary and instructed in its use. Group A patients will be instructed to bring all unused pills and their medication diary to the hospital on the day of surgery for assessment of compliance. During post-surgical cycles of lapatinib, all patients will be instructed to bring all unused pills and their medication diaries to each study visit for assessment of compliance.

4.3.1 Lapatinib Administration

Lapatinib is an oral drug. Patients should take the lapatinib dose on an empty stomach, either 1 hour before or 1 hour after meals. Doses of lapatinib should be taken 12 hours apart ± 2 hours.

If a patient misses or vomits a dose, he or she should be instructed not to take or make up that dose. A dose will be considered missed, and should not be made up, if more than 2 hours have passed from the time the dose is normally taken.

Group A patients, pre-surgery: On the day of surgery the dose should be taken ideally 3-5 hours before scheduled surgery but no more than 12 hours prior to surgery (the time tumor tissue is removed). One additional dose is permitted 12 hours after the fourth dose (± 2 hours) if unexpected logistical problems delay the surgery.

Grapefruit and grapefruit juice are prohibited while on this protocol.

4.4 General Concomitant Medication and Supportive Care Guidelines

Prohibited Concomitant Medication During Study

There must be a period of at least 10 days from discontinuation of prohibited drugs and initiation of therapy unless otherwise specified in the protocol. Requests for specific exceptions to the required wait time can be submitted to the ABTC Central Office by providing a pharmacological rationale that the washout period for a particular drug should be less than 10 days (or as specified in the protocol); this must be approved by the ABTC Central Office.

In vitro studies with human liver microsomes indicate that lapatinib is metabolized by CYP3A4 and CYP3A5, and to a lesser extent CYP2C19 and CYP2C8. **Co-administration of lapatinib with potent or moderate CYP3A4 inhibitors (including grapefruit juice) and all CYP3A4 inducers is prohibited.** Assess risk/benefit before co-administering lapatinib with weak CYP3A4 inhibitors. CYP3A4 inhibitors may decrease lapatinib metabolism (increasing levels); while CYP3A4 inducers may increase lapatinib metabolism (decreasing levels).

In human subjects, lapatinib inhibited CYP3A4 and CYP2C8 at clinically relevant concentrations. Avoid co-administration of lapatinib with drugs that are substrates of CYP3A4 or CYP2C8 and have narrow therapeutic windows.

Pgp inhibitors: the following drugs are in vivo substrates of the P-gp transporter and may not be administered to patients receiving lapatinib: aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan; clinically significant interactions have been demonstrated for the following drugs: digoxin, loperamide, saquinovir, and ritonavir.

Grapefruit and grapefruit juice are prohibited while on this protocol.

Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

Antiemetics

The use of any antiemetic deemed necessary for the care of the patient is allowed.

Anticonvulsants

For this study, patients may not be on enzyme-inducing anti-epileptic drugs (EIAED); patients who require anti-epileptic drugs (AED) may be on non-enzyme inducing anti-epileptic drugs (NEIAED). If a patient on this study protocol needs to have an AED started or needs to have a second AED added then only NEIAED should be used. There must be a $\geq$ 10 day period from discontinuation of an EIAED and initiation of therapy. In the event that an enzyme-inducing anti-epileptic drug must be used for a patient on study the patient will be removed from the protocol.

Antidiarrheal

The use of any antidiarrheal is permitted. Lapatinib-induced diarrhea is most commonly treated with loperamide. Patients should be educated about how to use loperamide. See also Supportive Care below for management of diarrhea.

Herbal and Non-Traditional Medications

No data exist regarding the interaction of lapatinib with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving lapatinib therapy.

Supportive Care

Diarrhea

Early diarrhea management for patients taking lapatinib must be initiated as soon as the first episode of diarrhea has occurred. Close monitoring and proactive management of diarrhea is essential. At the time of starting lapatinib, all patients should be given a prescription for loperamide or analogue, and be advised to keep the prescription/medication with them at all times. The patient should be clearly instructed to start loperamide promptly at the first signs of diarrhea. A dose of 4 mg loperamide must be given after first episode of diarrhea, and 2 mg every 4 hours or after every episode of unformed stool, until the patient is free from diarrhea for 12 hours. The maximum allowed daily dose of loperamide is 16 mg. The patient must contact the investigator as soon as possible after diarrhea starts.

For Grade 3 or 4 diarrhea or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration): use intravenous fluids as appropriate, consider hospital administration and use prophylactic antibiotics as needed (example fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is a fever or Grade 3-4 neutropenia.

Rash

There is no standard, known, or established treatment proven effective for drug-related skin rashes or changes due to lapatinib. If the rash is severe (1-3% of cases) then most commonly, a papular/pustular rash has been observed, which frequently improves even though the same dose of lapatinib therapy is continued uninterrupted. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation. **Oral retinoids should not be given because of theoretical concerns about negatively affecting the lapatinib mechanism of action.** Oral steroids are also strongly discouraged. Other options for treatment of significant rashes may be determined upon consultation with dermatologist.

5.0 TOXICITY

5.1 Toxicity Management and Dose Delay/Modification for Lapatinib

Dose delays and dose modification requirements for clinically significant adverse events or abnormal laboratory values assessed as unrelated to disease progression, intercurrent illness, or concomitant medications are defined in the following sections. Toxicities must have an attribution of possible, probable, or definite to lapatinib (see Section 9.2.2). Adverse events (AEs) should be treated with the appropriate maximum supportive care and should be clearly documented on the case report form.

Group A patients–pre-surgical treatment: Lapatinib is not dose-reduced for toxicities in the pre-surgical dosing period; if treatment is delayed for toxicity such that the patient cannot receive the four lapatinib doses according to the pre-surgical dosing schedule, or if

lapatinib is discontinued, the patient will be replaced in the cohort but may continue with post-surgical treatment provided toxicity from pre-surgical dosing resolves within protocol parameters.

All adverse events will be monitored and collected throughout the trial and documented based on CTCAE version 5.0. If there are three or more delays of scheduled surgery due to lapatinib-related serious adverse events (SAE) among the initial 8 patients; or if there are any surgical complications and delayed wound healing SAEs grade ≥3 considered lapatinib-related among the first three patients, ABTC investigators will consult with CTEP investigators and the pharmaceutical sponsor about such events. See Section 9.3 for SAE information.

5.2 Dose Modification/Reduction for Lapatinib

The dose levels and the general approach to lapatinib dose modification on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented on the case report form.

If multiple toxicities occur, dose modification decisions should be based on the most severe toxicity.

Dosing will be held until the toxicity has resolved as specified in Table 5.2.2, Dose interruption or discontinuation due to LVEF, and Table 5.2.3, Toxicity management / Dose discontinuation due to AEs. The maximum length of time that lapatinib can be held for treatment-related toxicity is 14 days. If treatment-related toxicity is not resolved in ≤ 14 days, the patient will be removed from treatment. After resolution, when dose reduction is permitted, the dose of lapatinib will be modified as stipulated below, with a maximum of 1 dose reduction. If there is any question, the ABTC Central Office and the Study Chair should be contacted.

Dose Reduction Table for Lapatinib

Dose Level	Lapatinib
Starting dose	2500 mg twice a day
First dose reduction	2000 mg twice a day

5.2.1 Severe Cutaneous Reactions

Severe cutaneous reactions have been reported with lapatinib. If life-threatening reactions such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions) are suspected, discontinue treatment with lapatinib.

5.2.2 Lapatinib dose modification for LVEF events

General instructions for cardiac monitoring

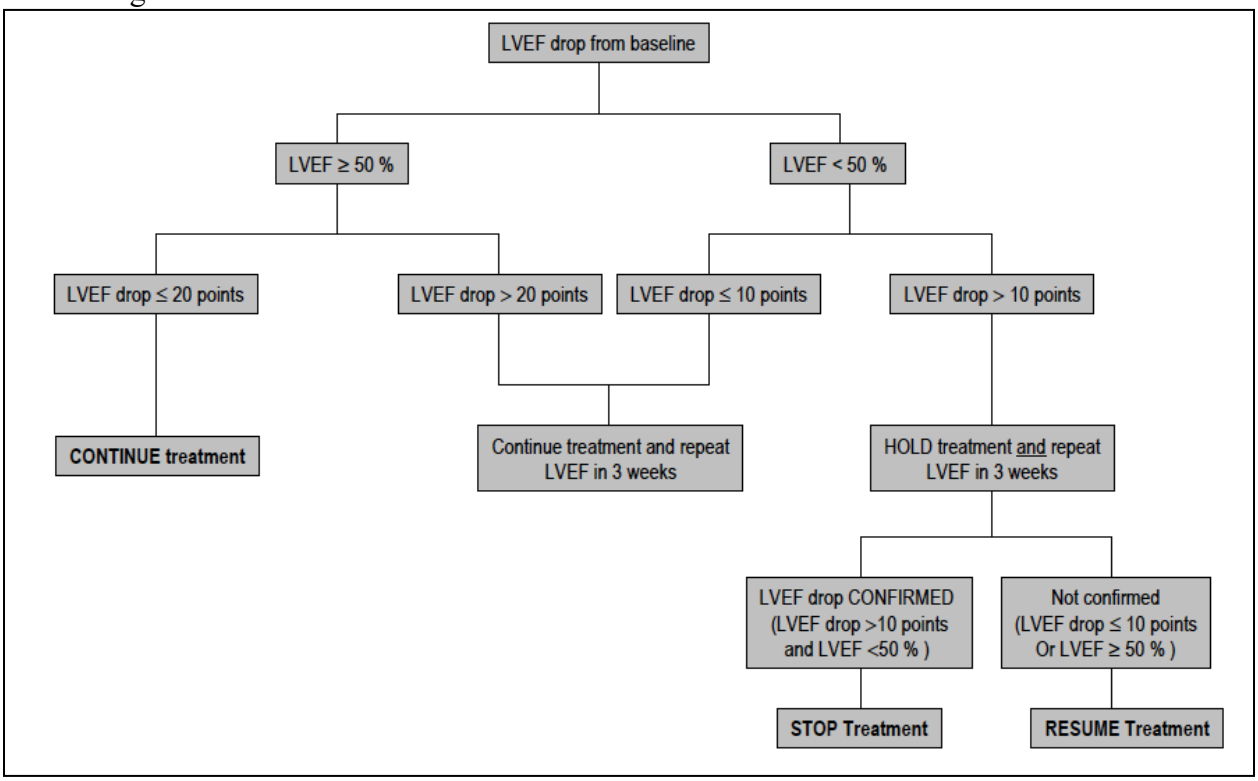
- All patients must have an LVEF measurement of at least 50% by echocardiography or MUGA scan (preferably echocardiography), within 21 days prior to treatment start.
- The method used for LVEF assessment in an individual patient should be the same throughout the trial.
- Echocardiography must be performed under the supervision of an experienced cardiologist, preferably at the same high-volume laboratory for the duration of the trial. The guidelines of the American Society of Echocardiography will be used.
- Subsequent scheduled LVEF assessments can be performed every 12 weeks during treatment. Follow up LVEF assessment after discontinuation of therapy should be obtained if the findings are abnormal.
- In addition, any patient who develops clinical signs or symptoms of cardiac failure should undergo an LVEF assessment and an ECG.
- If there are two dose interruptions for an ejection fraction decrease from baseline, discontinue lapatinib.

Table 5.2.2: Dose interruption or discontinuation due to LVEF

System Organ Class (SOC) in CTCAE	CTCAE Term	Instructions
Cardiac Disorders	If symptomatic, please utilize CTCAE term "Left ventricular systolic dysfunction (LVSD)" or "Heart failure," as appropriate	Permanently discontinue lapatinib.
Investigations	If asymptomatic, please utilize CTCAE term "Ejection fraction decreased"	Refer to Figure below and instructions above. If there are two dose interruptions for an ejection fraction (EF) decrease from baseline, discontinue lapatinib.

Algorithm for continuation and discontinuation of GW572016 (lapatinib) based on interval LVEF assessments for patients with New York Heart Association (NYHA) Class

I or II congestive heart failure.



Notes:

- Only one dose interruption for ejection fraction decrease will be allowed.
- All assessments will be compared to baseline ejection fraction at the start of the trial.

5.2.3 Lapatinib dose modification for non-cardiac AEs

Table 5.2.3:

Adverse Events	Grade	Action
Pneumonitis, Pulmonary fibrosis, Adult Respiratory Distress Syndrome (ARDS), Pulmonary edema (non-cardiogenic)	Grade 1 to 4	Patients who develop symptoms or signs suggestive of pulmonary infiltrates or pneumonitis, should have lapatinib interrupted while a thorough evaluation is performed. If pneumonitis is confirmed, permanently discontinue lapatinib. If other parenchymal abnormalities are confirmed and the relationship to lapatinib cannot be excluded, lapatinib must be permanently discontinued.
Rash	Grade 1	No dose modifications. **See "supportive care for rash."**

Adverse Events	Grade	Action
	Grade 2	If toxicity is unacceptable to patient or medically concerning, hold lapatinib until recovery to ≤ Grade 1 for up to 14 days. Restart at the same dose. If dose has previously been held for grade 2 toxicity and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ Grade 1. **See "supportive care for rash."** Resume at one dose reduction..
	Grade 3	Hold lapatinib until recovery to < Grade 1 for up to 14 days. **See "supportive care for rash."** Resume at one dose reduction.
	Grade 4 rash or toxic epidermal necrolysis (*e.g.*, Stevens-Johnson Syndrome, etc.)	Permanently discontinue lapatinib. **See "supportive care for rash."**
Diarrhea	Grade 1	Continue lapatinib, but start loperamide (initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool). It is suggested to continue loperamide until the subject is free from diarrhea for 12 hours. **See "supportive care for diarrhea."**
	Grade 2 to 4	Hold lapatinib until grade 1 or lower (up to 14 days). Start loperamide as above, and other measure. **See "supportive care for diarrhea."** Resume at one dose reduction.
Abnormal liver function tests (ALT, bilirubin)	Grade 1 or 2 abnormal ALT / bilirubin	Lapatinib must be discontinued permanently for patients with: 1. BOTH bilirubin and ALT abnormalities being of Grade 2 *OR* 2. EITHER bilirubin OR ALT abnormality is Grade 2 and accompanied by signs or symptoms which, in the opinion of the treating physician, are related to liver injury caused by lapatinib. (Such signs and symptoms may include abdominal pain, fever, jaundice, rash, eosinophilia or a performance status (PS) drop of ≥1 point from baseline.)
	Grade 3 to 4 abnormal ALT and / or bilirubin	Permanently discontinue lapatinib.
Other Grade 3 to 4 AEs or intolerable Grade 2 AEs due to lapatinib		Permanently discontinue lapatinib therapy.

5.3 Major Events

Major Events are non-treatment-related grade 3 and 4 hematologic and non-hematologic toxicities. Treatment should be discontinued for major events if lapatinib may further complicate the non-treatment-related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline). If non-treatment-related toxicity is not resolved in ≤

28 days, the patient will be removed from treatment. The ABTC Central Office should be consulted if it is not clear whether to continue or stop treatment.

5.4 Use of Hematologic Growth Factors

No growth factors (G-CSF or GM-CSF) are to be used prophylactically in this protocol. Clinicians caring for patients on this protocol are permitted to use these growth factors to provide optimal care for patients with severe neutropenia in accordance with the ASCO 27guidelines (JCO, 12, 1994: pp2471-2508). If these growth factors are used in the acute setting of neutropenia and infection (documented or suspected), they will not be utilized prophylactically in subsequent cycles and they will not subsequently be used in lieu of dose reduction of lapatinib.

5.5 Toxicity Criteria

All toxicities will be described and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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). See also Section 9.2.4, Recording of Adverse Events.

6.0 PHARMACEUTICAL INFORMATION

6.1 Lapatinib (GW572016, NSC 727989)

Chemical Name: N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2 furyl]-4-quinazolinamine

Other Names: GW572016F, lapatinib ditosylate, Tykerb®

Molecular Formula: $C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$

Molecular Weight: 943.48

Approximate Solubility: 0.007 mg/mL in water and 0.001 mg/mL in 0.1 N HCl at 25°C.

Mode of Action: Dual inhibitor of epidermal growth factor receptor (EGFR or ErbB1) and ErbB2 tyrosine kinases.

How Supplied: GlaxoSmithKline supplies and the NCI/DCTD distributes lapatinib as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. The tablets contain 405 mg of lapatinib ditosylate

monohydrate, equivalent to 250 mg lapatinib free base per tablet. The tablets are packaged into HDPE bottles with child-resistant closures containing 90 tablets per container.

Excipients present in the tablet include: Microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate.

The film-coat contains: Hypromellose methylcellulose, titanium dioxide, macrogol/PEG 400, Polysorbate 80, FD&C Yellow No. 6, and FCF aluminum lake.

Storage: Store intact bottles at controlled room temperature (15°C-30°C).

Stability: Shelf life surveillance studies of the intact bottle are on-going.

Route of Administration: Oral on an empty stomach (either 1 hour before or 1 hour after meals).

Method of Administration: Whenever possible, administer whole tablets. Lapatinib tablets have not been deliberately formulated to be dispersible tablets; however, in circumstances where dosing of whole tablets is not possible, see procedure below. **Tablet crushing is not recommended.**

For patients unable to swallow tablets, a suspension preparation in water or Kool-Aid can be made using the following procedure:

1. Prepare Lemonade or Tropical Punch Kool-Aid as directed on package.
2. Place 2 or 4 ounces of water or Kool-Aid in a glass container, then add the required number of lapatinib tablets for dose (up to six tablets per 2 to 4 ounces) to the container.
3. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 15 minutes or until it is fully dispersed.
4. Stir the container for 5 seconds then administer.
5. Rinse the container with 2 ounces of water or Kool-Aid and repeat the administration process.

(The lemonade mixture appears somewhat like orange juice whereas the tropical punch mixture appears like carrot juice.)

Potential Drug Interactions: *In vitro* studies with human liver microsomes indicate that lapatinib is metabolized by CYP3A4 and CYP3A5, and to a lesser extent CYP2C19 and CYP2C8. Co-administration of lapatinib with potent or moderate CYP3A4 inhibitors (including grapefruit juice) and all CYP3A4 inducers is prohibited. Assess risk/benefit before co-administering lapatinib with weak CYP3A4 inhibitors. CYP3A4 inhibitors may decrease lapatinib metabolism (increasing levels); while CYP3A4 inducers may increase lapatinib metabolism (decreasing levels).

In human subjects, lapatinib inhibited CYP3A4 and CYP2C8 at clinically relevant concentrations. Avoid co-administration of lapatinib with drugs that are substrates of CYP3A4 or CYP2C8 and have narrow therapeutic windows.

Pgp inhibitors: the following drugs are in vivo substrates of the P-gp transporter and may not be administered to patients receiving lapatinib: aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan; clinically significant interactions have been demonstrated for the following drugs: digoxin, loperamide, saquinovir, and ritonavir

For **Potential Risks of Lapatinib**, see Section 9.2.1, Comprehensive Adverse Events and Potential Risks list (CAEPR) for lapatinib.

6.1.1 Agent Ordering

Lapatinib may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

6.1.2 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. *See the NCI Investigator's Handbook on the CTEP web site for Procedures for Drug Accountability and Storage.).*

7.0 REGISTRATION PROCEDURES / PATIENT ENROLLMENT

This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and uses the Oncology Patient Enrollment Network (OPEN).

7.1 CTEP Registration

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

7.2 Site Registration

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the ABTC
- A valid IRB approval
- Compliance with all protocol-specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Downloading Site Registration Documents:

See ABTC website (www.abtconsortium.org).

Requirements for Site Registration:

- IRB approval (local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the ABTC. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

7.3 Patient Registration

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users enrolling patients to ABTC studies from 9 a.m. to 4:30 p.m. Eastern Time. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role in ABTC. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, site staff must check the ABTC website (www.abtconsortium.org) for protocol status and slot availability. Site staff must also use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot-reservation confirmation is obtained, and the ABTC Central Office has notified the site of the randomization assignment, site staff may then proceed to enroll patients to this study.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for credentialing in the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration and treatment assignment information. Please print this confirmation for your records. Upon completion of the registration process in OPEN, sites must contact the ABTC Central Office to obtain confirmation of the patient's registration and treatment assignment.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.0 SAFETY AND QUALITY ASSURANCE

8.1 Criteria for Response Assessment

Subjects with measurable disease will be assessed by the RANO (radiographic assessment in neuro-oncology) criteria (Wen et al. 2010). For the purposes of this study, subjects should be re-evaluated at the end of every 2 cycles (approximately every 8 weeks) with a contrast-enhanced cranial MRI scan. The response will be determined as outlined in the RANO criteria below.

The MRI obtained prior to starting post-surgery treatment cycles of lapatinib will be used as the baseline MRI for purposes of determining radiographic response.

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

Complete Response (requires all of the following):

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) Subjects must be off corticosteroids (or on physiologic replacement doses only).
e) Stable or improved non-enhancing (T2/FLAIR) lesions.
f) Stable or improved clinically.

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

Partial Response (requires all of the following):

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 corticosteroid 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 clinically.

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

Stable Disease (requires all of the following):

a) Does not qualify for CR, PR, or progression.
b) The designation of stable disease requires a minimum of 4-week duration.
c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

e) Stable clinically.

Progressive Disease (defined by any of the following):

a) ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative 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 adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.
e) Failure to return for evaluation due to death or deteriorating condition.
f) Clear progression of non-measurable disease.

* Stable doses of corticosteroids include patients not on corticosteroids.

8.2 Assessment of Response

Assessment of response will begin with the MRI performed just prior to *every odd-numbered* treatment cycle post-surgery**.** If during any scheduled MRI, the subject has a Complete Response or Partial Response, the MRI should be repeated prior to the next cycle. All scans are to be compared to the smallest measurement scan to date. The subject will then return to the every odd-numbered cycle schedule. This is required to confirm the duration of response. Subjects will be classified as responders if they have a minimum duration of response for 4 weeks at any time after the first post-surgery cycle of lapatinib. MRI scans of subjects showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression.

8.3 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs, and the performance of physical/neurological examinations, and ECGs.

8.4 Quality Assurance

Neuropathology: The neuropathologic diagnosis of (study disease) will be made at the respective institution. If any question arises regarding the accuracy of the neuropathologic diagnosis, slides (and pathological blocks, if necessary) will be reviewed by the central review pathologist. For protocols with "response" as an outcome, all patients with a documented complete response or partial response will have representative pathology slides undergo central review.

Neuroradiology: MRI scans of patients showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression.

Neuro-oncology: The local investigator at the participating institution will communicate to the ABTC Central Office any unexpected neurological effects such as change in seizure frequency, alteration in neuromuscular function, alteration in cognitive function, or fluctuations in serum anticonvulsant drug levels.

Adherence to protocol therapy: As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random; complete records must therefore be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given; any reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (MRI scan, lab reports, dated notes on measurements and clinical assessment, as appropriate).
- NCI Drug Accountability Records were maintained for this protocol.

9.0 MONITORING OF PATIENTS

9.1 Tables of Required Observations

Group A

	Baseline	Pre-Surgery	Day of Surgery	Post-Surgery	Post-Surgery Cycles	Pre-Odd Cycles	Pre-Even Cycles	Every 3 Cycles	Off Treatment (within 7 days)	30-Day Follow-Up
Lapatinib		6			6					
Adverse Event Evaluations			7	10		17	17		12	13
Glucocorticoids Dose	1			19		17			12	
MRI	1			19		17,18			12	
H&P/Neuro exam	1					17	17		12	
KPS	1					17	17		12	
Vital Signs	1,2					2,17	2,17		2,12	
CBC, platelets, Differential	1		11			17	17		12	
Serum Chemistry	1,3		3,14			3,17	3,17		3, 12	
APTT or PTT	1									
Serum Pregnancy Test	1,4									
Echocardiogram	1					16		16		
12-Lead Electrocardiogram	15									
Plasma Pharmacokinetics	8		8							
Fresh Tumor Tissue			9							
Archived Tumor Tissue	5									

1 – All baseline measurements must be done within 21 calendar days prior to start of treatment, unless otherwise indicated.
2 – Including blood pressure, respiratory rate, heart rate, temperature, weight, and height: height is required at baseline only.
3 – Albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
4 – Females with child-bearing potential must have a negative serum pregnancy test.
5 – Archived tumor tissue from initial surgery at diagnosis of high-grade glioma. See Section 9.5.2
6 – Four doses of lapatinib will be administered pre-operatively starting 2 days prior to the day of surgery with the last pre-operative dose taken 3-5 hours prior to scheduled surgery: see Section 4.1 for schedule. One additional dose is permitted if unexpected logistical problems delay surgery.
Post-operatively patients will receive lapatinib twice a day for two consecutive days every 7 days (2 days on/5 days off) in 28-day cycles. Patients are required to keep a pill diary. See Section 4.3.1.
7 – Patient should be seen on the day of surgery (prior to the the time of surgery) to evaluate for AEs.
8 – Plasma specimens for pharmacokinetics will be obtained at baseline and pre- and post-surgical resection. See Section 9.5.3 for details.
9 – Fresh tumor tissue for correlative studies will be collected day of surgery. See Section 9.5.1, 9.5.2, and 9.5.4 for details.
10 – Within 3 days post-surgery.
11 – Within minus 1 day
12 – Evaluations done within +7 days of off-treatment date unless indicated; do not repeat: if MRI within 14 days of off-treatment date; if H&P /neuro-exam, KPS, labs within minus 5 days of off-treatment date.
13 – Adverse Events must be followed for at least 30 days from the last dose of lapatinib, until resolution, within +14 days.

14 – After last dose of study drug, prior to surgery
15 – 12-lead electrocardiogram (ECG) must be performed within 2 weeks prior to start of treatment, with QTc ≤470 msec.
16 – LVEF must be monitored every 12 weeks (3 cycles), including pre-Cycle 1, to ensure that LVEF does not decline below the institutional lower limit of normal. See Section 5.2.2.
17 – Within minus 5 calendar days of starting cycle
18 – For Cycle 1 only, perform scan only if patient will start cycle >21 days from post-operative scan (patient must have scan within ≤21 days of Cycle 1 start). Record glucocorticoid dose at time of MRI.
19 – Perform MRI 1-3 days post-operatively. Record glucocorticoid dose at time of MRI

Reference Group

	Baseline	Day of Surgery	Post-Surgery	Post-Surgery Cycles	Pre-Odd Cycles	Pre-Even Cycles	Every 3 Cycles	Off Treatment (within 7 days)	30-Day Follow-Up
Lapatinib				9					
Adverse Event Evaluations			7		10	10		12	13
Glucocorticoids Dose	1		8		10			12	
MRI	1		8		10,14			12	
H&P/Neuro exam	1				10	10		12	
KPS	1				10	10		12	
Vital Signs	1,2				2,10	2,10		2,12	
CBC, platelets, Differential	1				10	10		12	
Serum Chemistry	1,3				3,10	3,10		3,12	
APTT or PTT	1								
Serum Pregnancy Test	1,4								
Echocardiogram	1				11		11		
12-Lead Electrocardiogram	15								
Fresh Tumor Tissue		6							
Archived Tumor Tissue	5								

1 – All baseline measurements must be done within 21 calendar days prior to start of treatment, unless otherwise indicated.
2 – Including blood pressure, respiratory rate, heart rate, temperature, weight, and height: height is required at baseline only.
3 – Albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
4 – Females with child-bearing potential must have a negative serum pregnancy test.
5 – Archived tumor tissue from initial surgery at diagnosis of high-grade glioma. See Section 9.5.2
6 – Fresh tumor tissue for correlative studies will be collected day of surgery. See Section 9.5.1, 9.5.2, and 9.5.4 for details.
7 – Within 3 days post-surgery.
8 – Perform MRI 1-3 days post-operatively. Record glucocorticoid dose at time of MRI.
9 – Post-operatively patients will receive lapatinib twice a day for two consecutive days every 7 days (2 days on/5 days off) in 28-day cycles. Patients are required to keep a pill diary. See Section 4.3.1.
10 – Within minus 5 calendar days of starting cycle
11 – LVEF must be monitored every 12 weeks (3 cycles), including pre-Cycle 1, to ensure that LVEF does not decline below the institutional lower limit of normal. See Section 5.2.2.
12 – Evaluations done within +7 days of off-treatment date unless indicated; do not repeat: if MRI within 14 days of off-treatment date; if H&P /neuro-exam, KPS, labs within minus 5 days of off-treatment date.
13 – Adverse Events must be followed for at least 30 days from the last dose of lapatinib, until resolution, within +14 days.
14 – For Cycle 1 only, perform scan only if patient will start cycle >21 days from post-operative scan (patient must have scan within ≤21 days of Cycle 1 start). Record glucocorticoid dose at time of MRI.
15 – 12-lead electrocardiogram (ECG) must be performed within 2 weeks prior to start of treatment, with QTc ≤470 msec.

9.2 Adverse Events

Patients will be evaluated for toxicity if they have received at least one dose of lapatinib.

The timely reporting of adverse events (including toxic deaths) is required by the Food and Drug Administration. The reporting of toxicities is part of the data reporting for this study.

The following Adverse Events must be reported to the ABTC Central Office and the NCI in the manner described in addition to the Institution's Institutional Review Board.

All adverse events will be mailed/emailed to the ABTC Central Office by the investigative site in a timely manner. See Section 12.0 – Records to be Kept.

All CTEP/NCI Adverse Drug Reactions will be reported to the ABTC Central Office and CTEP/NCI within 24 hours of known event (unless otherwise specified).

9.2.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) For Lapatinib (GW572016, NSC 727989)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 6120 patients.* Below is the CAEPR for Lapatinib (GW572016).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to Lapatinib (GW572016) (CTCAE 5.0 Term) [n= 6120]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
	Abdominal pain		***Abdominal pain (Gr 2)***
	Anal mucositis		***Anal mucositis (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Flatulence		***Flatulence (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	***Hepatic failure (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
		Ejection fraction decreased	
		Electrocardiogram QT corrected interval prolonged	***Electrocardiogram QT corrected interval prolonged (Gr 2)***
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***

Adverse Events with Possible Relationship to Lapatinib (GW572016) (CTCAE 5.0 Term) [n= 6120]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Epistaxis		
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
		Pneumonitis	
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		
		Erythema multiforme	
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***
	Hot flashes		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on lapatinib (GW572016) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lapatinib (GW572016) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Pericarditis; Sinus tachycardia
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dysphagia; Gastritis; Hemorrhoids; Ileus; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; GGT increased; INR increased; Lymphocyte count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperphosphatemia; Hypoalbuminemia; Hypoglycemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Flank pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Cerebrospinal fluid leakage; Depressed level of consciousness; Dizziness; Intracranial hemorrhage; Nervous system disorders - Other (altered dream pattern); Nervous system disorders - Other (sleep walking); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Syncope
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Pregnancy loss
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Oropharyngeal pain; Pleural effusion; Pulmonary edema; Pulmonary fibrosis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Pain of skin; Skin and subcutaneous tissue disorders - Other (onychocryptosis); Skin and subcutaneous tissue disorders - Other (seborrheic dermatitis); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (hypovolemia)

Note: Lapatinib (GW572016) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2.2 Definition - Adverse Event (AE)

Adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

9.2.3 Relationship

The Investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:

- *Unrelated*
  The adverse event is clearly not related to the investigational agent(s).

- *Unlikely*
  The adverse event is doubtfully related to the investigational agent(s).

- *Possible*
  The adverse event may be related to the investigational agent(s).

- *Probable*
  The adverse event is most likely related to the investigational agent(s).

- *Definite*
  The adverse event is clearly related to the investigational agent(s).

9.2.4 Recording of Adverse Events - ABTC AE Form

- **Document on ABTC Adverse Event Data Form**

  - The Investigator will monitor each patient closely for the development of adverse events and record all such events on the ABTC AE Case Report Form. Each single sign or symptom must be reported separately.

  - **CTCAE term (AE description) and grade**: The descriptions and grading scales found in the 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). **You must use one of the CTCAE criteria to define your event.**

  - Adverse events not included in the CTCAE should be reported under "Other" within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual. New adverse events may be submitted to the CTEP Help Desk at ncictcaehelp@mail.nih.gov for annual evaluation by the CTCAE Change Management Committee.

  - Abnormal lab results which are graded by NCI CTCAE will be recorded on the ABTC Laboratory Cover Sheet along with documented attribution, not on the AE form. However, if an action was taken due to this abnormality (e.g. RBC transfusion due to low Hgb) this would be recorded on the AE form also.

All adverse events should be followed up in accordance with good medical practice. Abnormalities of laboratory events which, in the opinion of the investigator, constitute adverse events (even if not serious) should be followed.

9.3 Serious Adverse Events and Expedited Adverse Event Reporting

9.3.1 Definition – Serious Adverse Event (SAE)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event

3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3.2 CTEP Adverse Event Reporting System (CTEP-AERS)

- **Use CTEP-AERS Web Application and Document on ABTC AE Form**

  - Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov).

  - This study will utilize the descriptions and grading found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for toxicity and Serious Adverse Event Reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. You must use one of the CTCAE criteria to define your event.

    Serious Adverse Events not included in the CTCAE should be reported under "Other" within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual.

  - Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

  - In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

  - CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization,

Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

Secondary Malignancy:

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

9.3.3 Expedited Reporting Requirements

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease Progression" in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

9.3.4 Other Reporting

Any Serious Adverse Event, as described in Section 9.3.1, including death due to any cause, which occurs during this study must be reported immediately (within 24 hours) to the ABTC Central Office.

A phone call must be made to:

SERENA DESIDERI
ABTC DATA COORDINATOR
OFFICE: 410-614-4400

FAX: 410-614-9335
(OR JOY FISHER, ABTC MANAGER: 410-955-3657 / 410-599-4610)

These events also must be reported by the Investigator to the appropriate Institutional Review Board (IRB).

Patients who are removed from study due to adverse events should be followed until the adverse event has resolved or stabilized. Copies of relevant documentation, such as laboratory reports, should be kept with the patient's study records.

9.4 Data Reporting

This study will be monitored by the Clinical Data Update System (CDUS). The ABTC Central Office is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

9.5 Correlative Studies

Table 9.5: Synopsis of Correlative Studies

Measurement	Technique	Participants	Timing of collection	Collection requirements	More Information
EGFR gene amplification in Tumor: (**Integral Biomarker**)	Fluorescence In-Situ Hybridization (FISH) on FFPE	Group A and Reference Group	Archived sample	5 **UNSTAINED SLIDES** (4 micron thick) from most recent surgery	Section 9.5.2
Ki67 and other IHC measurements **(Exploratory)**	IHC of FFPE tumor tissue	Group A and Reference Group	Archived and protocol surgery	20 **UNSTAINED SLIDES** each from archived tumor block and protocol surgery tumor block: 5 micron thick	Section 9.5.2
Lapatinib blood concentrations **(Exploratory)**	LC-MS/MS analysis of plasma samples	Group A	Before and During Protocol surgery	Three **BLOOD SAMPLES**: one sample collected before starting lapatinib and two samples collected during tumor resection	Section 9.5.3
Lapatinib tumor concentration **(Integrated)**	LC-MS/MS analysis of fresh frozen tissue	Group A	Protocol Surgery	Combined Total Tumor Tissue Required for both tumor concentration and EGFR phosphorylation (*FROZEN TUMOR SPECIMEN WILL BE SPLIT INTO ALIQUOTS AT CENTRAL SITE*): At least 500mg from contrast enhancing region. When possible, also at least 100 mg from non-contrast enhancing region	Section 9.5.5
EGFR phosphorylation in Tumor **(Integrated)**	Electro-chemiluminescence of fresh frozen tissue	Group A and Reference Group	Protocol surgery		Section 9.5.6
Ex-vivo sensitivity of tumor sphere cultures **(Exploratory)**	Trypan Blue Assay	Group A and Reference Group	Protocol Surgery	When possible, 500 mg or more of *additional* Tumor Tissue for Tumor Sphere Culture	Section 9.5.7

Biospecimen Criteria for Patient Replacement: patients on protocol will be replaced if any of the following tissue factors apply:

Surgical sample:

- Less than 500 mg of frozen tissue obtained from the contrast enhancing portion of the tumor
- Frozen tissue does not contain tumor
- Time from tumor removal to freezing greater than 5 minutes
- No paraffin tumor block or fewer than 20 unstained slides available.

Archived surgical sample:

- Fewer than 20 unstained slides available

Blood PK (applies to Group A only):

- Blood samples not obtained at time of surgery

9.5.1 Tissue Requirements for Protocol Surgery: Group A and Reference Group

Every effort should be made to collect adequate amounts of tissue.

The minimum **tissue requirements** to be collected from participants at the time of surgery include:

- 500 mg of fresh frozen tissue from the contrast enhancing portion of the tumor. This sample will be used for the determination of the primary objectives of the study for both the tumor drug distribution endpoints (Section 9.5.5) and EGFR phosphorylation endpoints (Section 9.5.6)

- 100 mg of fresh frozen tissue from the non-contrast enhancing portion of the tumor (if low risk of inducing neurological injury). This sample will be used in an exploratory fashion regarding tumor drug distribution and EGFR phosphorylation.

- If sufficient tissue is available, 500 mg or more of additional enhancing tissue (for tumor sphere cultures)

The **remainder of the sample** should be fixed in formalin and processed for routine paraffin embedding and sectioning at the site, per usual site protocols in pathology.

The precise location in the tumor from which these specimens were obtained and the precise time should be recorded. Depending on local site's capabilities, if a common navigation system is used for surgical localization, segmentation of the tumor using 3D visualization software is recommended for accurate sampling localization. Using this

reconstructed model, a representative screenshot is requested demonstrating the location of the resected tissue. If not possible, then a screenshot of the MRI showing the location of the resected tissue should be included.

9.5.2 Archived and Protocol Surgery Paraffin Tumor Tissue (Group A and Reference Group)

Prior to registration (Integral Biomarker): Archived tumor tissue from the most recent prior resection of high-grade glioma (pre-treatment) will be collected from all patients who are being screened for enrollment. **Evidence of EGFR amplification from this analysis will be considered a necessary inclusion criteria for enrollment.** EGFR gene amplification must be determined through a CLIA-certified FISH assay. Results of the EGFR-FISH assay must be sent to the ABTC Central Office to confirm patient eligibility. Determination of EGFR gene dosage through next-generation sequencing assay will not suffice for patient eligibility.

After completion of protocol surgery: 20 consecutively cut unstained slides each from the archived sample and the protocol surgery will be requested for exploratory IHC analysis including KI67 Analysis. These can be shipped together in separate containers along with the associated pathology report from the institution of collection. Notification of the delivery must be made by e-mail to both Dr. Ingo K. Mellinghoff (email: mellingi@mskcc.org) and Carl Campos (e-mail: camposc@mskcc.org). Include the name of the courier and the tracking no. in the email.

Please ship to:

Dr. Ingo Mellinghoff
Memorial Sloan Kettering Cancer Center
Zuckerman Research Building, Room Z-703
408 East 69th Street
New York, NY. 10021
Telephone: + 1 (646) 888-2766
Fax: + 1 (646) 422-0856

9.5.3 Plasma Pharmacokinetics: Group A Participants

Obtaining single plasma samples before and after the surgical procedure will allow the average drug concentration in plasma during the surgical procedure to be calculated. The pretreatment baseline plasma sample is needed to document that there are no potential compounds that could interfere with the detection of the drug in plasma or tumor samples. Obtaining these plasma samples is an important component of the drug distribution study and it does not have an additional objective per se. Samples are not being collected to characterize the pharmacokinetic behavior of the drug.

A single blood sample will be obtained at baseline, prior to the first dose of lapatinib. In addition, single blood samples will be obtained on the day of surgery at convenient times, both shortly before and shortly after the tumor resection.

For all pharmacokinetic plasma samples, draw 3 mL of blood into a plastic plasma collection tube with spray-coated sodium heparin at each of the time points specified. Promptly mix the specimen by gently inverting the collection tube several times and then place it on wet ice. Centrifuge the sample at 1,100-1,300 x g for 10 min at 4°C within 5-10 min after collection. Remove the plasma from the blood cells using a pipette and distribute it in equal volumes into two self-standing polypropylene cryogenic tubes with external threads. Affix a computer-printed label (protocol no., patient no., sample no., scheduled sample time) to each cryotube. Completely cover the label with protective cryogenic freezer tape (Fisher catalog no. 11-867B). Place the tubes on crushed dry ice until stored in a freezer maintained at -70°C.

The concentration of lapatinib in study samples will be determined by the ABTC Pharmacokinetics Center using an LC-MS/MS assay. The analytical method will be validated and applied to the analysis of study samples as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf).

Send complete sets of plasma samples from each patient by overnight courier to the address listed below. Place the sample tubes within a zip lock plastic bag. Fill a seamless styrofoam container with at least 3 inches of dry ice, place the plastic bag containing the samples on top of the dry ice, and completely cover the bag with an additional 3 inches or more of dry ice. Seal the styrofoam container within a tight-fitting cardboard shipping box. Seal a copy of the sample collection time form for each set of samples within a zip-lock plastic bag and place the bag on top of the styrofoam container before the external shipping box is sealed. Send the samples on a Monday, Tuesday, or Wednesday by overnight courier for delivery by 10:00 AM on the following day. Notification of the delivery must be made by e-mail to both Dr. Jeffrey G. Supko (email: jsupko@partners.org) and Sarah Hilderbrand (e-mail: slhilderbrand@partners.org). Include the name of the courier and the tracking no. in the email.

Please ship to:

Dr. Jeffrey G. Supko
Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

9.5.4 Handling and Shipping of Frozen Tumor for tumor concentration and EGFR phosphorylation

Neurosurgeons at all participating sites are trained in the collection of biospecimens for pharmacokinetic and pharmacodynamic analyses. Tumor samples will be frozen within 5 min of collection.

The research nurse will notify the laboratory of scheduled sample collections, preferably giving at least 24-h notice, to allow sufficient time to set up laboratory supplies, collect relevant clinical information, and ensure rapid transport of specimens to the laboratory for placement at -80ºC (or lower) after collection.

Promptly after excision, rinse the tissue with ice-cold phosphate buffered saline and gently blot on Whatman filter paper to remove surface fluid. Place the tissue into pre-chilled 2.0 mL cryogenic tubes (Fisher catalogue no. 12-565-291). The label must contain the patient ID no. and information identifying the region from which the tissue was excised. Snap freeze the specimen by placing the tube in liquid nitrogen or a dry ice/ethanol bath and record the time of freezing in the Batch Record. Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of minutes and seconds elapsed in the Batch Record. Samples will be transferred to a -80°C freezer or liquid nitrogen tank for storage until shipment to the PD processing laboratory. Record the date and time specimens are placed at -80ºC.

Just prior to shipment, specimen tubes will be placed into an 81-place freezer box and then in a shipping container with sufficient dry ice to maintain the samples at -20°C for at least 72 hours. Specimens will be shipped via FedEx for delivery by 10 AM the next day (FedEx First Overnight). Seal the box and print and attach the shipping address onto the outside of the shipping container and label the contained as containing biohazardous specimens. Record the shipping date, time, tracking number, and shipping information in the Batch Record. Notification of the delivery must be made by e-mail to both Dr. Ingo K. Mellinghoff (email: mellingi@mskcc.org) and Carl Campos (e-mail: camposc@mskcc.org). Include the name of the courier and the tracking no. in the email.

Ship all frozen tumor samples to:

Ingo Mellinghoff, MD
Memorial Sloan Kettering Cancer Center
Zuckerman Research Building, Room Z-703
408 East 69th Street
New York, NY. 10021
Telephone: + 1 (646) 888-2766
Fax: + 1 (646) 422-0856

Once specimens arrive at the Mellinghoff laboratory, they will be immediately placed at -80ºC (or lower). Dr. Mellinghoff's group will collect all samples, cut a 5 µM section from each specimen and then perform H&E staining. Histopathological review of the H&E stain will be performed by a board-certified neuropathologist at Memorial Sloan-Kettering Cancer Center. Only samples with a tumor cell content > 80 % as determined by a pathologist will be used for further analyses. Each frozen tumor specimen that

passes histopathological Q/C will be split into two samples, one for the determination of intratumoral lapatinib concentrations (Section 9.5.5) and one for the determination of EGFR phosphorylation (Section 9.5.6).

9.5.5 Tumor Samples for Intratumoral Drug Distribution: Group A

The specimens for the determination of intratumoral lapatinib concentration will be shipped to the ABTC Pharmacokinetics Center by the Mellinghoff Laboratory following the shipping guidelines in Section 9.5.3. The concentration of lapatinib in study samples will be determined by the ABTC Pharmacokinetics Center using an LC-MS/MS assay, also described in Section 9.5.3.

Biopsy specimens selected for drug concentration measurement should be at least 0.05 cm^3 (50 mg) intact sections of tumor tissue. To the extent possible, at least one biopsy sample should be resected from a contrast enhancing region of the tumor and another from a non-contrast enhancing region for drug level analysis. These samples must be clearly identified accordingly.

Intratumoral lapatinib concentrations will be measured in fresh frozen tumor aliquots in two batches.

- the first batch of samples (patients # 1-8) will be used for the interim futility analysis and will be run after the initial eight patients. Study enrollment will continue if three or more of these eight tumor samples show an intratumoral lapatinib concentration of > 1.5 μM.
- the second batch of tumor samples (patient # 9-18) will be performed after enrollment has been completed.

Lapatinib concentrations in plasma at the time of tumor resection will also be determined (Section 9.5.3) and this data will be used to calculate a lapatinib tumor/plasma ratio.

9.5.6 Tumor Samples for Determination of EGFR phosphorylation in Tumor Tissue: (Group A and Reference Group)

Determination of EGFR protein levels and EGFR phosphorylation will be performed in the Mellinghoff Laboratory. Samples will be lysed in sample buffer with protease and phosphatase inhibitors which has been optimized by MesoScale Discovery to minimize decay of the protein and phosphosignal (http://www.mesoscale.com). All clinical trial samples will be run through the mesoscale electrochemiluminescent assay in a single batch. Residual samples will be aliquoted and frozen. All specimens will be handled and stored to minimize decay of the phospho-signal. Further Details regarding the EGFR Mesoscale Assay are provided in Appendix IV. Performance characteristics of this pharmacodynamic assay will be validated in additional laboratory experiments and presented for CTEP review before the specimens from the trial are analyzed.

9.5.7 Tumor Sphere Cultures

Glioma Tumor Sphere Lines will be prepared from fresh tumor samples whenever possible (i.e., if there is 500 mg or more of additional enhancing tissue) at each participating ABTC site. The consortium has successfully derived glioma tumor sphere cultures in the context of a prior clinical trial (ABTC 0906).

Whenever possible, at least 500 mg grams of viable tissue will be processed for neurosphere studies. The sterility of the specimen should be preserved while it is minced gently into 0.5 cm cubes in the operating room which optimizes conditions for cellular survival, prevents tube breakage/leakage, and maintains cells at low temperature while avoiding freezing of cells. In brief, a pre-labeled 25cc tube should be filled to the top with a low-glucose, serum-free, buffered transport medium and **placed immediately on wet ice in the operating room**. The specimen should then be inserted into a protective tube to prevent breakage, sealed in a Ziploc bag, and packed **on wet ice** in a pre-labeled styrofoam container with relevant identifying information. The starting and ending times of resection should be noted by personnel at the institution and included in the specimen identification form.

Specimens for tumor sphere cultures must be shipped immediately from the participating ABTC site to the Mellinghoff Laboratory. Specimens will be shipped via FedEx on the same day for delivery by 10 AM the next day (FedEx First Overnight). Seal the box and print and attach the shipping address onto the outside of the shipping container and label the container as containing biohazardous specimens. Record the shipping date, time, tracking number, and shipping information in the Batch Record.

Notification of the delivery must be made by e-mail to both Dr. Ingo K. Mellinghoff (email: mellingi@mskcc.org) and Carl Campos (e-mail: camposc@mskcc.org). Include the name of the courier and the tracking no. in the email.

Ship all tumor samples to:

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New York, NY. 10021
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Fax: + 1 (646) 422-0856

Upon receipt, the specimen will be immediately logged into the Oncore database and transported to the Mellinghoff laboratory. Within 20 minutes of **arrival at the Mellinghoff Laboratory**, sterile, refrigerated specimens will be processed into neurosphere cultures. Tumor specimen samples are washed in cold PBS twice, then manually dissociated and placed in Accumax (Innovative Cell Technologies) for 15 min under sterile conditions. Cells are subsequently washed and filtered through a 100-µm

strainer and plated in NeuroCult NS-A proliferation media (Stemcell Technologies) supplemented with 10 ng/mL rhbFGF for all experimental conditions in the study. Initial cultures are also supplemented with 20 ng/mL rhEGF. Cells are incubated at normal oxygen levels at a temperature 37.0 °C and 5% CO2 (Szerlip et al. 2012).

Lapatinib sensitivity will be determined in the Mellinghoff Lab using a Trypan Blue Exclusion Assay (Vivanco et al. 2012).

10.0 OFF TREATMENT/OFF STUDY CRITERIA

Each subject has the right to withdraw from the study at any time without prejudice. The investigator may discontinue any subject's participation for any reason, including adverse event or failure to comply with the protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.).

Should a subject withdraw from the study, the reason(s) must be stated on the case report form, and a final evaluation of the subject should be performed.

Patients who go off treatment must be followed for adverse events (AEs) for at least 30 days from the last dose of lapatinib.

10.1 Off Treatment Criteria

1. Disease Progression: Remove patient from protocol therapy at the time progressive disease is documented. Disease progression is defined as: Progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, etc.) or a greater than 25% increase in the measurement of the tumor by MRI scan. If neurologic status deteriorates, on a stable or increasing dose of steroids, or if new lesions appear on serial MRI, further study treatment will be discontinued

2. Adverse Event:
   - Intercurrent illness that prevents further administration of treatment
   - Patients who experience unacceptable toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

3. Patient Withdrawal: Patient's refusal to continue treatment: in this event, document the reason(s) for withdrawal.

4. Non Compliance: Failure to comply with protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.)

5. Physician Decision: If at any time the treating physician feels constraints of this protocol are detrimental to the patient's health remove the patient from protocol therapy.

6. Protocol Defined Delay:
   - Patients who experience a treatment-related toxicity causing a delay in treatment > 14 days
   - Delay in protocol > 28 days for major events or other non-treatment related delays

7. Death

10.2 Off Study Criteria

Patients will only be off study at the time of death. All patients will be followed for survival every 2 months for the first two years from the off treatment date; after 2 years, patients will be followed every 6 months until death. Survival status may be obtained by phone call, clinic visit, or medical records (e.g. physician notes/laboratory results of clinic or hospital visit).

11.0 STATISTICAL CONSIDERATIONS

This is an open-label, multicenter, early phase clinical trial to evaluate whether lapatinib, when given on a pulsatile dosing schedule, will reach an intratumoral concentration of 1.5 μM or higher in 70% of patients with recurrent and surgically accessible EGFR-amplified high-grade glioma. It will also determine whether this lapatinib dosing regimen will achieve 80% reduction in ratio of phosphorylated to total EGFR in tumor tissue in 70% of patients with recurrent and surgically accessible EGFR-amplified high-grade glioma.

Primary Endpoints:

- Lapatinib intratumoral concentration (PK)
- Ratio of pEGFR/total EGFR (PD) in tumor tissue

Primary Objectives and Sample Size:

The first primary objective is to evaluate whether pulsatile lapatinib, when given on the pulsatile dosing schedule, can reach an intratumoral concentration of 1.5 μM or higher in 70% of patients with recurrent and surgically accessible EGFR-amplified high-grade glioma.

Initially eight patients will be treated with pulsatile lapatinib and the intratumoral concentration of lapatinib will be analyzed.

- if no more than 2 patients achieve adequate tumor lapatinib concentration of 1.5 μM or higher, the trial will be stopped early for futility. The probability of early stopping for futility is 68% with a true null of 25% while maintaining only 1.1% probability of early termination for a true rate of 70% (the target).
- if 3 or more of the initial 8 patients reach an intratumoral drug concentration level of 1.5 μM or higher, 10 additional patients will be enrolled into the study.
- if 8 or more of the 18 patients treated with pulsatile lapatinib achieve intratumoral lapatinib concentrations of at least 1.5 μM, the PK objective will be met. This

design has 98% power to detect a true rate of 70% from a null of 25% in achieving lapatinib intratumoral concentration level of 1.5 μM with a false positive rate of 0.05.

The PD study will be pursued after the initial 8 patients' PK objective is met.

The primary PD objective is to test the hypothesis that 70% of patients will achieve 80% reduction in ratio of phosphorylated to total EGFR after pulsatile lapatinib treatment assuming a null of 25% patients. A ratio of pEGFR/total EGFR at 80% reduction from a median value from the untreated reference group will be considered as the putative threshold to qualify a near complete inhibition of EGFR (at 80%). If at least 9 (50%) of the 18 treated patients demonstrate a pEGFR/total EGFR ratio which corresponds to at least an 80% reduction compared to the median pEGFR/total EGFR ratio for the 15 patients enrolled on the reference arm, the PD objective will be met. This design yields 98% power to detect a true 70% rate of near complete (80%) EGFR inhibition and it yields a false positive rate of 2% for a true 25% rate of such EGFR inhibition.

Initial safety monitoring: All adverse events will be monitored and collected throughout the trial and documented based on CTCAE version 5.0. If there are three or more delays of scheduled surgery due to lapatinib-related Serious Adverse Events among the initial 8 patients; or if there are any surgical complications and delayed wound healing SAEs grade ≥3 considered lapatinib-related among the first three patients, ABTC investigators will consult with CTEP investigators and the pharmaceutical sponsor about such events. An internal safety monitoring evaluation will be conducted after the first three patients complete their first follow-up visit after surgery.

Reference Group (for primary PD study):

15 lapatinib-naïve patients with recurrent and surgically accessible EGFR-amplified high-grade glioma will be enrolled as a reference group for the PD evaluation to establish the threshold of 80% reduction in the ratio of pEGFR/total EGFR. After the initial 8 patients are enrolled into Group A, eligible patients will be sequentially assigned to either treatment group or reference group. The sample size of 15 patients on the reference arm yields 90% confidence that the observed median falls between the true 30^{th} and 70^{th} percentiles of the pEGFR/total EGFR distribution for untreated patients.

To avoid batch effect and other variations through tumor sample processing, all tumor samples will be processed at the same time at the Mellinghoff Lab, Memorial Sloan-Kettering Cancer Center.

Secondary and Exploratory Objectives:

1. All treatment or surgically related AEs will be reported descriptively. A proportion of toxicity grade >=3 will be estimated using binomial distribution.

2. To estimate inhibition of tumor cell proliferation (KI-67), descriptive statistics will be used for summarizes results and Box plots could be used to present the difference between the treated and untreated groups.
3. To characterize ex-vivo sensitivity of tumor sphere cultures to lapatinib, the *ex-vivo* sensitivity of tumor sphere cultures established from surgical specimens to pulsatile lapatinib is defined by a minimum of 20% reduction in cell proliferation as measured by cell titer glow in the pulsatile lapatinib group compared to the untreated group. Fisher's exact test will be used for testing a difference in the proportion between the two groups.
4. To estimate tumor objective response rate as the evidence of biological activity among patients with recurrent GBM treated by lapatinib, the proportion of patients who had objective PR or CR during the course of the treatment will be estimated along with 95% confidence intervals using the exact binomial method.
5. To estimate overall survival (OS), the survival time is defined from the date of treatment start to the date of death. Patients who have not expired by the data analysis cutoff date will be censored at their last date known to be alive. The Kaplan-Meier method will be used to estimate overall survival probability and median time of survival along with a 95% confidence interval.
6. To estimate progression-free survival, The progression is defined a radiographic tumor progression, a >=25% increasing from baseline scan with a confirmatory scan at least 8 weeks apart from the initial scan that tumor progression was observed. The date of progression is defined as the date of initial scan deemed tumor progression. The Kaplan-Meier method will be used to estimate progression-free survival probability and median time of survival along with a 95% confidence interval. The progression-free survival at 6-month is defined as: patient, who started treatment, is alive and progression free at the time of 6 month follow-up. The probability of 6-month progression-free survival will be estimated using binomial distribution.

12.0 RECORDS TO BE KEPT

Data collection for this study will be done exclusively through CTEP's Medidata Rave.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of the ABTC must have the Rave CRA role in RSS at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive an invitation from iMedidata to activate their account. If you have any questions please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

- All data are due within 14 days of evaluation time point. Please see Section 9.1 for evaluation time points.
- Serious Adverse Events, PHONE IMMEDIATELY, SEE SECTION 9.3

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14.0 COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as

appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

15.0 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the investigator that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly confidential and not be publicly available. The investigator is responsible for the retention of the patient log and patient records.

APPENDIX I – PATIENT MEDICATION DIARY

Pre-Surgical Treatment (Group A patients): Lapatinib 2500 mg, 12 hours apart, during the 2 days prior to surgery and on the day of surgery

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take 4 doses of **lapatinib 2500 mg, 12 hours apart (±2 hrs.), starting 2 days prior to surgery and on the morning of surgery**. If surgery is delayed you may take one additional dose of lapatinib.
   Dose: take ___ 250 mg tablets.
2. Take on an empty stomach, either 1 hour before or 1 hour after meals.
3. Do not consume grapefruit or grapefruit juice during participation on this study.
4. Record the date, the time you took the tablets, and the number of tablets that you took. Record missed or skipped dose(s).
5. Bring this form and any remaining lapatinib tablets when you return for surgery.

Day	Timeframe	Date	Time	# of 250mg tablets	Comments
2 days prior to surgery	Evening				
1 day prior to surgery	Morning				
	Evening				
Day of Surgery: 3-5 hrs. prior to surgery	Morning				
(additional dose if surgery delayed)					

Patient's Signature _____

Date _____

Post-Surgical Treatment: Lapatinib 2500 mg twice a day for 2 consecutive days, every 7 days during 28-day cycles

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **lapatinib _____ mg twice a day, 12 hours apart (±2 hrs.), for 2 days in a row every week (7 days), during each 4-week cycle**.
   Dose: take _____ 250 mg tablets.
2. Take on an empty stomach, either 1 hour before or 1 hour after meals.
3. Do not consume grapefruit or grapefruit juice during participation on this study.
4. Record the date, the time you took the tablets, and the number of tablets that you took. Record missed or skipped dose(s). Vomited doses should not be replaced/repeated.
5. Bring this form and your bottles of lapatinib tablets when you return for each appointment.

Week	Day	Date	Time of morning dose	Time of evening dose	# of 250 mg tablets taken	Comments
1	1					
	2					
	3		No dose	No dose	-	
	4		No dose	No dose	-	
	5		No dose	No dose	-	
	6		No dose	No dose	-	
	7		No dose	No dose	-	
2	8					
	9					
	10		No dose	No dose	-	
	11		No dose	No dose	-	
	12		No dose	No dose	-	
	13		No dose	No dose	-	
	14		No dose	No dose	-	
3	15					
	16					
	17		No dose	No dose	-	
	18		No dose	No dose	-	
	19		No dose	No dose	-	
	20		No dose	No dose	-	
	21		No dose	No dose	-	
4	22					
	23					
	24		No dose	No dose	-	
	25		No dose	No dose	-	
	26		No dose	No dose	-	

	27		No dose	No dose	-	
	28		No dose	No dose	-	

Patient's signature _____

APPENDIX II – INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient _____ is enrolled on a clinical trial using the experimental agent **lapatinib**. *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

Lapatinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Lapatinib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme in question is CYP3A4 and *certain agents are considered "inducers" which when taken will more rapidly clear lapatinib and make it less effective and agents are considered "inhibitors" which when taken slow down the clearance of lapatinib and make it more likely to cause side effects.*
- Lapatinib must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any prescribed medicines *over-the-counter medications or supplements* that are considered "strong inducers/inhibitors or substrates of ***CYP3A4***
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent lapatinib. This clinical trial is sponsored by the NCI. Lapatinib interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	Lapatinib interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX III – INFORMATION ON EGFR MESOSCALE ASSAY

Sample Collection and Shipping: All patient samples will be collected at member institutions of the Adult Brain Tumor Consortium (ABTC). Neurosurgeons at all participating sites are trained in the collection of biospecimens for pharmacokinetic and pharmacodynamic analyses. The clinical trial protocol specifies detailed Standard Operating Procedures (SOP) for the Frozen Tumor collection and handling. Tumor samples will be frozen within 5 min of collection. Samples will be transferred to a -80°C freezer or liquid nitrogen tank for storage until shipment to the Mellinghoff Laboratory.

Sample Processing and Batching: Dr. Mellinghoff's group will collect all samples, cut a 5 μM section from each specimen using a cryotome housed in the Mellinghoff Laboratory, and then perform H&E staining and histopathological review of each specimen. Only samples with a tumor cell content > 80 % as determined by a pathologist will be used for further analyses. Samples will be lysed in sample buffer with protease and phosphatase inhibitors which has been optimized by MesoScale Discovery to minimize decay of the protein and phosphosignal (http://www.mesoscale.com).

In preliminary experiments, we have confirmed the stability of the analyte in EGFR amplified human glioblastoma xenograft tumor samples processed under similar conditions as the primary human tumor samples.

EGFR amplified GBM xenografts and lysates from several human cancer cell lines, were used to establish the dilution linearity and robustness of the MSD assay. Lysates from multiple cancer cell lines (A431, COS-7, SKOV3) were included as MSD Assay Controls. Lysates were tested at 4-fold dilutions to provide an assortment of various assay signal levels. Prior to lysis, cells were treated to induce tyrosine phosphorylation (positive control) or inhibit phosphorylation (negative control).

Samples will be run on 96 well plates which have been pre-coated with antibodies against total EGFR and phosphorylated EGFR (tyrosine 1173), respectively. In our previous study (PMID: 22588883), we used mesoscale plates which were coated with antibodies against EGFR and phospho-EGFR in two different quadrants of the same well. Because this approach can result in substrate competition which could jeopardize linearity and matrix tolerance, our future study will separate this assay into two plates, one plate coated with an antibody against total EGFR and one plate coated with an antibody against phospho-tyrosine 1173-EGFR. Each well will be loaded with 20 μg of total protein.

All clinical trial samples will be run through the mesoscale electrochemiluminescent assay in a single batch. Residual samples will be aliquoted and frozen. All specimens will be handled and stored to minimize decay of the phospho-signal. Each well on the 96-well plate will be loaded with 20 μg of protein from tumor or cell line lysate. *Samples from EGFR amplified GBM xenografts, that were used during assay development, will be included in the analysis*.