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Title: A Phase II Study of Dose-Dense Temozolomide and Lapatinib for Recurrent Low-Grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma

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Investigator Roles:

A. *Obtain information by intervening or interacting with living individuals for research purposes*

B. *Obtaining identifiable private information about living individuals*

C. *Obtaining the voluntary informed consent of individuals to be subjects*

D. *Makes decisions about subject eligibility*

E. *Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*

F. *Studying, interpreting, or analyzing de-identified data or specimens for research purposes*

G. *Some/all research activities performed outside NIH*

Commercial Agents:

Temozolomide and Lapatinib are commercially available.

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PRÉCIS

Background:

- Although relatively uncommon, ependymoma can occur at any age group although the tumors of the posterior fossa are much more common in the pediatric population and spinal cord tumors are more common in young to middle age adults. Anaplastic ependymomas are more common in adults
- There have only been a limited number of reports describing chemotherapy treatments for patients with recurrent ependymoma, either low grade or anaplastic. As a consequence, optimal therapy for this group remains unknown. Traditionally, combination chemotherapy regimens have been used, often containing either carboplatin or cisplatin. Many of these treatment programs were associated with a high incidence of moderate to severe toxicity
- Given the paucity of established treatments for recurrent ependymomas in adults, we propose a study that uses a combination of an established cytotoxic agent, temozolomide with a small molecule tyrosine kinase inhibitor. Temozolomide was chosen because it has an established track record in treating primary brain tumors, it has a good safety profile and recent data suggest that certain dosing schedules may modulate tumor cell resistance via the MGMT mechanism. Given the recent studies in glioblastoma that correlate MGMT methylation status with outcome, modulating MGMT activity may have a significant impact on response
- Additionally, we plan to target the ERBB1 and the ERBB2 pathways using lapatinib on a continuous daily dosing schedule

Objectives:

- To determine the efficacy of the combination of temozolomide and lapatinib in recurrent brain ependymoma and anaplastic ependymoma as measured by median progression-free survival.

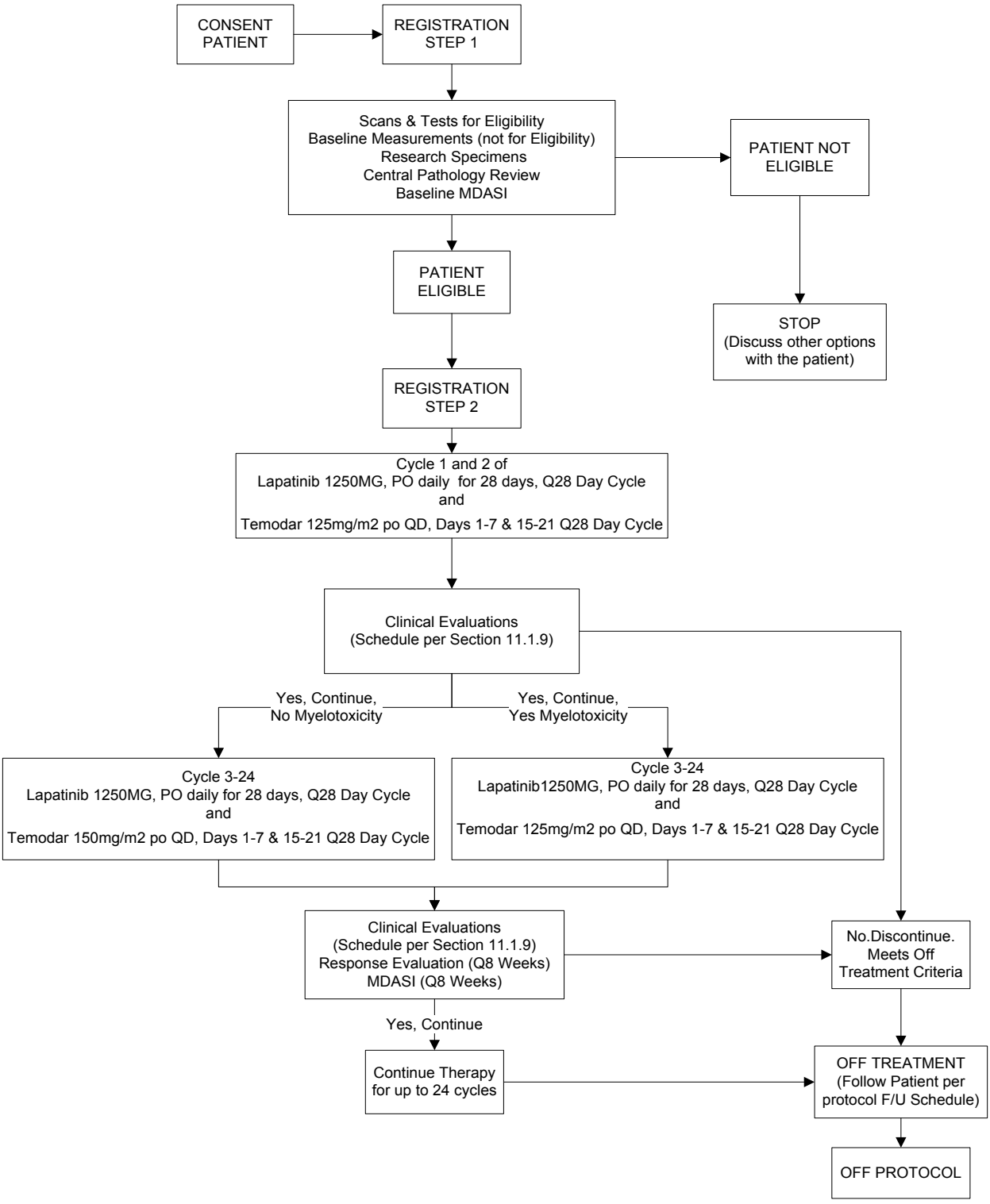
Eligibility:

- Histologically proven ependymoma or anaplastic ependymoma. There must be pathologic or imaging confirmation of tumor progression or regrowth.
- Patients must be on a steroid dose that has been stable or decreasing for at least 5 days.
- Karnofsky performance status ≥ 70
- Age ≥ 18
- No severe, active comorbidity
- No condition that impairs ability to swallow pills

Design:

- This is a phase II study to determine the efficacy of the combination of temozolomide and lapatinib in recurrent brain ependymoma and anaplastic ependymoma as measured by median progression-free survival.
- Eligible patients will receive 2 cycles of the combination of temozolomide and lapatinib. The temozolomide will be administered at a dose of 125 mg/m2 as a single daily dose on days 1-7 and 15-21 of a 28-day cycle. The lapatinib will be given as a single daily dose of 1250 mg orally. Patients who do not experience any grade 1 or greater myelotoxicity will be eligible to have the temozolomide dose increased to 150 mg/m2 as a single daily dose on days 1-7 and 15-21 of a 28-day cycle. The lapatinib dose will not be increased.
- Patients who exhibit response to protocol therapy and have not experienced any significant or intolerable toxicities may continue to receive protocol therapy up to a maximum number of 24 cycles.
- Patients that are showing sustained Complete Response (CR), Partial Response (PR) or Stable Disease (SD) may continue post protocol single agent therapy with lapatinib. Post-protocol lapatinib supply may be obtained through Glaxo Smith-Kline (GSK). Patients on post protocol single agent lapatinib will have follow up visits every 2 months for survival assessment and radiographic evaluation of disease per MRI or CT scan.

STUDY SCHEMA



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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the efficacy of the combination of temozolomide and lapatinib in recurrent brain ependymoma and anaplastic ependymoma as measured by median progression-free survival.

1.1.2 Secondary Objectives

1.1.2.1 To determine the efficacy of the combination of lapatinib and temozolomide as measured by objective response in patients with measurable disease.

1.1.2.2 To determine the adverse event profile and tolerability of the combination of lapatinib and temozolomide in patients with recurrent ependymoma

1.1.2.3 To correlate response, either by objective response or progression-free survival at 12 months with EGFR expression, PTEN expression and MGMT gene promoter methylation status.

1.1.2.4 Determine the efficacy of the combination of lapatinib and temozolomide in spinal cord ependymoma as a component of a pilot study.

1.1.2.5 Patient Related Outcome Objectives:

- To evaluate longitudinal changes in symptom measures and determine the impact of the therapy on these parameters.
- To measure symptom burden over the course of therapy to evaluate differences between patients individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between responders and nonresponders.
- To describe the variability of symptom severity longitudinally over the treatment course and follow-up period.

1.2 BACKGROUND AND RATIONALE

1.2.1 Ependymoma

Ependymoma remains a relatively uncommon primary brain tumor in adults. Recent CBTRUS data (1998-2002) compiling incidence of both ependymoma and anaplastic ependymoma in patients age 20 and above reveals a rate of approximately 0.27 per 100,000 population(CBTRUS 2005). Contrast this with glioblastoma where the annual incidence is approximately 9.4 per 100,000. Ependymomas are found throughout the CNS in the supratentorial (ST), posterior fossa (PF), and spinal (SP) compartments and they affect both pediatric and adult populations. The classification of ependymomas is based on the degree of pleomorphism, tumor cells proliferation, cellularity, and tumor infiltration into surrounding brain tissue. The WHO classifies ependymomas into low grade labeled “ependymoma” (also called a “WHO grade II ependymoma) and the more malignant designation “anaplastic ependymoma” (also classified as a “WHO grade III ependymoma”)(Kleihues and Cavenee 2000).

The causes of ependymoma are not known. Although relatively uncommon, the disease can occur at any age group although the tumors of the posterior fossa are much more common in the pediatric population and spinal cord tumors are more common in young to middle age adults. Anaplastic ependymomas are more common in adults. A series of genetic changes have been reported in these tumors, although a wide variability between tumors has been reported. Furthermore, patients can be initially diagnosed with an anaplastic ependymoma or these malignant tumors can develop from the malignant transformation of the lower grade ependymoma. This underscores the importance of genetic changes in the formation of the disease, the biologic behavior including malignant transformation and the potential utilization of these characteristic molecular changes as treatment targets. The variable patterns of histology and clinical presentation of ependymoma, and the separation of pediatric and adult oncology services, have hindered efforts to coordinate clinical trials in this disease. As a result, no new therapeutic approaches have been identified to treat ependymoma during last 20 years and up to 40% of patients remain incurable](Brandes, Cavallo et al. 2005; Merchant and Fouladi 2005).

Currently, the standard therapy for newly diagnosed low-grade ependymoma includes total surgical excision followed by radiation therapy. Complete surgical resection is often not possible because of the location of the tumor and the concern for damage to surrounding eloquent brain during surgery. The situation is even more critical for patients with anaplastic ependymomas because of the higher proliferative rate and greater propensity for tumor infiltration into surrounding normal brain, preventing any possibility of complete tumor removal by surgery. For patients with the more aggressive anaplastic ependymoma, chemotherapy is often administered either before or after the radiation in the hope that infiltrating tumor cells will be eliminated. Unfortunately, even for patients with low-grade ependymoma, survival can be poor when the tumor is not totally surgically resected.

1.2.2 Treatment of recurrent ependymoma

There have only been a limited number of reports describing chemotherapy treatments for patients with recurrent ependymoma, either low grade or anaplastic. As a consequence, optimal therapy for this group remains unknown. Traditionally, combination chemotherapy regimens have been used, often containing either carboplatin or cisplatin. Many of these treatment programs were associated with a high incidence of moderate to severe toxicity.

A recent publication by Brandes and colleagues underscores some of the limitations in determining the optimal treatment for recurrent disease(Brandes, Cavallo et al. 2005). They report on the treatment of 28 adults who had recurrent ependymoma (n = 17) or anaplastic ependymoma (n = 11) after initial treatment with surgery and radiation. Half of the patients had undergone multiple tumor resections. A wide variety of regimens were used ranging from single agent temozolomide to the “8 in 1” regimen that combines 8 different chemotherapy agents. For their analyses, they looked at the composite group as well as a comparison of patients treated with or without cisplatin. No overall differences were noted based on the use of cisplatin. Furthermore, the overall objective response rate was 20% (CR and PR). The 12 month progression free survival rate was 44% (95% CI, 29-68%). The median time to progression was 9.9 months. These data provide a benchmark for subsequent clinical trials evaluating treatments for adults with recurrent ependymomas.

There have been anecdotal reports of response of ependymoma to temozolomide. The study by Brandes included 4 patients who received this either as single agent (n = 3) or in combination with cisplatin (n = 1)(Brandes, Cavallo et al. 2005). All patients were reported to have stable disease as their best response. A single case report describes a patient with recurrent anaplastic ependymoma with a greater than 10 year response to temozolomide therapy(Rehman, Brock et al. 2006). There is no published literature on the use of signal transduction modulating agents, save for a recent phase I study of the farnesyltransferase inhibitor lonafarnib in patients with recurrent primary pediatric brain tumors(Kieran, Packer et al. 2007). A single patient with a recurrent ependymoma did achieve stable disease with this regimen.

Recent correlative laboratory studies have carefully examined the molecular profiles of both pediatric and adult ependymomas. Distinct profiles of gene expression were uncovered that were primarily based on tumor location, with less difference in expression pattern noted between the pediatric and adult tumor samples.

1.2.3 Potential molecular targets in ependymoma

Several studies have been performed examining the spectrum of molecular profiles in ependymoma. These studies often examine a wide variety of tumors including grade II and III ependymomas, myxopapillary ependymomas. These series often include pediatric and adult tumors as well as those from spinal cord, posterior fossa and supratentorial locations. Most studies demonstrate specific molecular patterns that distinguish tumors by location with the largest differences noted between tumors arising within the spinal cord compared with those of brain origin. There are reports that find some distinct changes in comparing supra- from infratentorial tumors however this is much less striking.

Cytogenetic studies report aberrations on chromosome 22 in a high percentage of tumors, with either monosomy or 22q deletion (Lamszus, Lachenmayer et al. 2001; Suarez-Merino, Hubank et al. 2005). Intracranial tumors are reported to have a gain of 1q and chromosomal losses on 6q, 9 and 13(Korshunov, Neben et al. 2003). In comparison, spinal cord ependymomas have been reported to have gains on chromosome 7(Korshunov, Neben et al. 2003). Specific microarray analysis has shown increased expression of putative oncogenes such as WNTSA, as well as genes involved in cell cycle regulation, cell adhesion and proliferation(Suarez-Merino, Hubank et al. 2005). More recently, promoter methylation analysis has been performed on ependymoma cells uncovering that genes involved in apoptosis, such as TRAIL, are frequently methylated(Michalowski, de Fraipont et al. 2006). However, these studies also show that the MGMT gene is not commonly methylated, which may impact sensitivity of ependymoma to alklyating agent chemotherapies.

Recent, comparative genomic hybridization studies demonstrated that 90% of ependymomas had increased expression of EGFR(Gilbertson, Bentley et al. 2002). Furthermore, immunohistochemical analysis showed increased levels of intracellular EGFR in nearly 60% of intracranial ependymoma and this was highly correlated with a poorer prognosis ($P = 0.002$). Interestingly, although the rate of high expression of EGFR was the same in spinal cord tumors, there was no correlation with outcome. These studies suggest that EGFR may be a suitable target for treating intracranial ependymomas.

Additional studies have shown increased expression of ERBB2 and ERBB4 in pediatric intracranial ependymomas(Gilbertson, Bentley et al. 2002). Also, a polymorphism has been

detected in the promoter region of the PDGFRα gene that alters the binding of the transcription factor, ZNF-148, suggesting that the PDGFR pathway may be important in the development of some ependymomas(De Bustos, Smits et al. 2005). Therefore, the PDGFR pathway may also be a potential therapeutic target.

1.2.4 Study proposal

Given the paucity of established treatments for recurrent ependymomas in adults, we propose a study that uses a combination of an established cytotoxic agent, temozolomide with a small molecule tyrosine kinase inhibitor. Temozolomide was chosen because it has an established track record in treating primary brain tumors, it has a good safety profile and recent data suggest that certain dosing schedules may modulate tumor cell resistance via the MGMT mechanism. Given the recent studies in glioblastoma that correlate MGMT methylation status with outcome, modulating MGMT activity may have a significant impact on response.

Prolonged dosing of temozolomide using a dose-dense schedule has been shown to reduce MGMT activity in peripheral blood mononuclear cells(Tolcher, Gerson et al. 2003). Therefore, this strategy which has shown potential benefit in recurrent malignant glioma, may enhance the activity of temozolomide in ependymoma. In recurrent glioblastoma, response (as measured by 6-month progression free survival)l to conventional dosing of temozolomide was 21% (Yung, Albright et al. 2000). In comparison, a "week-on, week-off" schedule resulted in a 46% 6-month progression free survival rate(Wick, Felsberg et al. 2007). A similar dosing schedule is proposed for this study.

Additionally, we plan to target the ERBB1 and the ERBB2 pathways using lapatinib on a continuous daily dosing schedule. Given the recent results described above demonstrating a high percentage of ependymomas expressing high levels of EGFR (ERBB1) as well as ERBB2, these are logical targets. The concept of potential additive or synergistic benefit of combining a cytotoxic agent with a cytostatic agent has been established in brain tumor treatments. Conventional dosing of temozolomide shows better response when combined with either isotretinoin (6-month PFS = 31%) or marimastat (6-month PFS = 42%)(Groves, Puduvalli et al. 2002; Jaeckle, Hess et al. 2003).

Recently, studies have been performed on tumor tissues from patients with glioblastoma who were treated with EGFR inhibitors (either erlotinib or gefitinib). Two studies demonstrated a correlation of response with either EGFR overexpression or the presence of the EGFRVIII mutation, but only when the PTEN gene or protein was present(Haas-Kogan, Prados et al. 2005; Mellinghoff, Wang et al. 2005). It is not known whether these results are translatable to ependymoma. Therefore, in addition to the clinical trial, a correlative study will be performed. Tumor tissue will be analyzed for the following markers:

MGMT methylation status
EGFR amplification
EGFR vIII mutation
PI3K pathway activation

This correlative study may help define the tumors that are optimally treated with the combination of temozolomide and lapatinib. Furthermore, this study will further define the frequency of these molecular changes in adult ependymoma.

1.2.5 Temozolomide overview

Temozolomide, an oral alkylating agent with good penetration of the central nervous system, has been evaluated in patients with glial malignancies. Initial studies evaluated the efficacy of temozolomide in patients with recurrent glioblastoma and anaplastic glioma. A large, randomized phase II study by Yung and colleagues treated patients with recurrent glioblastoma with either temozolomide (200 mg/m^2 days 1-5 of a 28-day cycle) or procarbazine (150 mg/m^2 28 day-on, 28-day off schedule) (Yung, Albright et al. 2000). The study demonstrated only a modest objective response rate for both regimens (approximately 5%), but a superior 6-month progression-free survival rate for temozolomide (21% vs. 9%) was found. In the pre-radiation setting, a phase II study demonstrated a good objective response rate (complete plus partial response = 41%) in patients with glioblastoma during the four monthly cycles of treatment, using 200 mg/m^2 on days 1 to 5 of a 28-day cycle. However, the responses were not durable in many cases and the median progression-free survival rate was 3.8 months. Overall survival for patients on this study was 13.1 months, similar to most reports of treatment in newly diagnosed patients. This suggests that the neoadjuvant temozolomide chemotherapy likely had little overall benefit. However, these results did demonstrate definite activity of temozolomide for glioblastoma.(Gilbert, Friedman et al. 2002)

Stupp and colleagues performed a phase III trial in patients with newly diagnosed glioblastoma, administering a daily lower dose (75 mg/m^2) of temozolomide every day during the course of radiation therapy, followed by 6 months of adjuvant chemotherapy at the standard single-agent dose of 200 mg/m^2 for days 1 to 5 of a 28-day cycle.(Stupp, Mason et al. 2005) This study, performed by the EORTC and the NCIC, randomized patients with newly diagnosed glioblastoma to receive either radiation therapy alone or concurrent radiation and temozolomide followed by 6 months of adjuvant temozolomide. The study demonstrated a statistically significant improvement in median survival for the combination treatment arm (12.1 vs. 14.6 months) as well as a significant increase in 2-year survival (10% vs 26%). Eighty-eight percent of the patients received the full course of concurrent temozolomide with radiation. Approximately 40% of patients received the full 6 cycles of temozolomide after the completion of the radiation (adjuvant therapy). Tumor progression was the most prominent cause of treatment cessation. The chemoradiation treatment was well tolerated, with an incidence of grade 3 or 4 hematologic toxicity of < 4%. This chemoradiation regimen has been widely accepted as the new standard of care for patients with newly diagnosed glioblastoma.

As described above, incorporation of a dose-dense strategy for recurrent primary brain tumors is supported by the results of a recently reported clinical trial that treated patients with recurrent malignant glioma with the week on/week off dosing schedule of temozolomide at a dose of 150 mg/m^2 /day. This study reported a 6-month progression free survival rate of 46%, which compares favorably with the 6-month PFS rate of 21% reported with conventional 5 day of a 28 day cycle of temozolomide (Yung, Albright et al. 2000; Wick, Felsberg et al. 2007).

1.2.6 Lapatinib overview

Lapatinib acts as a dual inhibitor of both ErbB1(EGFR) and ErbB2 (HER2) tyrosine kinase activity. As a member of the 4-anilinoquinazoline class of kinase inhibitors, Lapatinib is thought to react with the ATP binding site of EGFR/ErbB2, resulting in inhibition of autophosphorylation and subsequent proliferative signaling (Shewchuk, Hassell et al. 2000). The ErbB family consists of four closely related growth factor receptor tyrosine kinases. The family is comprised of ErbB1

(EGFR/HER), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). All members of the ErbB family share a common extracellular ligand-binding domain, a single membrane-spanning region and a cytoplasmic tyrosine kinase domain (reviewed in (Yarden and Sliwkowski 2001) and (Burgess, Cho et al. 2003)). A ligand for ErbB2 has not been identified, while ErbB3 lacks tyrosine kinase activity. Ligand binding to EGFR, ErbB3 or ErbB4 induces these inactive monomers to undergo an array of homo- or heterodimerization with other members of the ErbB family. ErbB2 is the preferred heterodimeric partner for all ErbB receptors, resulting in a complex that is endocytosed at one half to one third the rate of other EGFR dimers (Graus-Porta, Beerli et al. 1997; Hendriks, Opresko et al. 2003). ErbB dimerization leads to receptor autophosphorylation and subsequent activation of the tyrosine kinase domain. The signaling characteristics of the ErbB family are thought to be strongly interdependent.

EGFR expression by tumor cells has been linked with aggressive tumor growth, disease progression, poor survival, and poor response to therapy. Overexpression of EGFR has been reported in a number of epithelium-derived carcinomas including head and neck, colorectal, lung, esophageal, gastric, and breast carcinoma. In a similar manner, ErbB2 has been reported to be overexpressed in 15-30% of invasive ductal breast cancer and has been associated with increased proliferation, poor clinical outcome, and altered responsiveness to various adjuvant therapies (Allred, Mohsin et al. 2001) Activation of either EGFR or ErbB2 initiates a series of signaling cascades that includes mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), Akt, and p70S6K.

1.2.6.1 Mechanism of Action

Lapatinib has been shown to be a potent and selective dual inhibitor of EGFR (ErbB1) and ErbB2 tyrosine kinase activity with IC_{50} values of 10.2 and 9.8 nM, respectively(Rusnak, Lackey et al. 2001). Lapatinib has demonstrated selective growth inhibition of human cell lines (head and neck, breast, and gastric) in vitro (IC_{90} values <2.26 μM or 1313 ng/mL) with no outgrowth observed up to 18 days following cessation of treatment. Growth inhibition corresponded with the ability of Lapatinib to inhibit phosphorylation of Akt.

These studies suggested that inhibition of EGFR by Lapatinib resulted preferentially in cell growth arrest, while inhibition of ErbB2 led to cell growth arrest and apoptosis after 72 hours. Treatment with Lapatinib leads to arrest of tumor cell growth and/or apoptosis, even in the presence of saturating concentrations of epidermal growth factor (EGF). Treatment of tumor xenografts resulted in inhibition of activation of EGFR, erbB2, Erk1/2, and Akt (Xia, Mullin et al. 2002).

1.2.6.2 Preclinical Studies

The ability of Lapatinib to inhibit the growth of EGFR-overexpressing cell lines (IC_{50} <0.16 μM) was observed to be equal to that of other EGFR inhibitors being tested in clinical trials (e.g. gefitinib/Iressa™ or erlotinib/Tarceva™). With the exception of ErbB4, Lapatinib was >300-fold more selective towards ErbB2 and EGFR kinase inhibition than to other kinases tested. Lapatinib demonstrated potent growth inhibition of human breast ductal (BT474) and head and neck (HN5) tumor xenografts in mice. A dose response inhibition was observed in both models receiving Lapatinib (30 or 100 mg/kg twice daily orally for 21 days). Complete inhibition of tumor growth was seen in mice receiving 100 mg/kg (Rusnak, Lackey et al. 2001).

1.2.6.3 Effects on Signal Transduction

Lapatinib has been shown to inhibit Erk1/2 and Akt phosphorylation (pErk and pAkt) in both EGFR and erbB2-expressing cell lines (BT474 and HN5). The ability of Lapatinib to inhibit pAkt was associated with a 23-fold increase in the percentage of cells undergoing apoptosis compared to control cells. Similarly, Lapatinib treatment of BT474 and HN5 xenografts in mice also resulted in inhibition of Erk1/2 and Akt phosphorylation. These results suggested that Lapatinib treatment of EGFR/erbB2 expressing tumors could lead to inhibition of downstream signaling events(Xia, Mullin et al. 2002).

A study of human breast cancer cell lines that overexpress EGFR or erbB2 (SUM102, SUM149, SUM185, and SUM225) reported that treatment with Lapatinib resulted in inhibition of cell proliferation that was associated with inhibition of Erk phosphorylation. Inhibition of Erk phosphorylation also correlated with radiosensitization of cell lines pretreated with Lapatinib(Zhou, Kim et al. 2004)

1.2.7 Rationale for use of Lapatinib in Ependymomas

As described above in section 1.3, comparative genomic hybridization studies demonstrated that 90% of ependymomas had increase expression of EGFR(Gilbertson, Bentley et al. 2002). Furthermore, immunohistochemical analysis showed increased levels of intracellular EGFR in nearly 60% of intracranial ependymoma and this was highly correlated with a poorer prognosis ($P = 0.002$). Similarly, a high rate of expression of EGFR was also seen in spinal cord tumors. These studies suggest that EGFR may be a suitable target for treating intracranial ependymomas.

Additional studies have shown increased expression of ERBB2 and ERBB4 in pediatric intracranial ependymomas(Gilbertson, Bentley et al. 2002). Also, a polymorphism has been detected in the promoter region of the PDGFRα gene that alters the binding of the transcription factor, ZNF-148, suggesting that the PDGFR pathway may be important in the development of some ependymomas(De Bustos, Smits et al. 2005). Therefore, the PDGFR pathway may also be a potential therapeutic target. Additionally, because heterodimerization of ErbB family receptors may lead to downstream signaling, agents that block activation of multiple ErbB family members may hold significant advantages. By inhibiting the kinase activity of ERBB1 and ERBB2, Lapatinib, may have a significant effect on the PI3K and RAS-ERK signaling cascades, which may in turn, have an effect on tumor growth

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Histologically proven ependymoma or anaplastic ependymoma. There must be pathologic or imaging confirmation of tumor progression or regrowth. The patient's histologic diagnosis must be confirmed on Central Pathology Review prior to registration Step 2.

2.1.1.2 The patient must have at least 1 block of tissue available or 15 unstained slides at a minimum, for central pathology review and molecular profiling of the tissue sample.

2.1.1.3 History and physical examination, including neurologic examination, within 2 weeks prior to registration.

2.1.1.4 Patients must be able to undergo brain or spine MRI scans with intravenous gadolinium, based on tumor location(s) within 14 days prior to registration.

2.1.1.5 Patients must be on a steroid dose that has been stable or decreasing for at least 5 days. If the steroid dose is increased between the date of imaging and registration, a new baseline MRI is required.

2.1.1.6 Karnofsky performance status ≥ 70

2.1.1.7 Age ≥ 18

2.1.1.8 CBC/differential obtained within 14 days prior to registration, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500/mm3
- Platelets ≥ 100,000 cells/mm3
- Hemoglobin ≥ 10.0 gm/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 is acceptable)
- White blood cell count (WBC) ≥ 3,000/mcL.
- Adequate liver function within 14 days prior to registration, defined as follows: SGPT (ALT) < 2.5 times the upper limit of normal, Bilirubin ≤ 1.6 mg/dL
- Adequate renal function within 14 days prior to registration, defined as follows: Creatinine < 1.7 mg/dL

2.1.1.9 Patients must have recovered from the toxic effects of prior therapy, and there must be a minimum time of:

- 28 days from the administration of any investigational agent
- 28 days from administration of prior cytotoxic therapy with the following exceptions:
- 14 days from administration of vincristine
- 42 days from administration of nitrosoureas
- 21 days from administration of procarbazine
- 7 days from administration of non-cytotoxic agents [e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count)].
- 28 days from prior radiation therapy.

2.1.1.10 Patients must have recovered from the effects of surgery and a minimum of 14 days must have elapsed from the day of surgery to the day of registration. For core or needle biopsy, a minimum of 7 days must have elapsed prior to registration.

2.1.1.11 Residual disease following resection of recurrent tumor is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, an MRI should be done no later than 96 hours in the immediate postoperative period or at least 4 weeks postoperatively, within 14 days prior to registration. If the "within 96-hour of surgery" scan is more than 14 days before registration, the scan needs to be

repeated.

2.1.1.12 Patients must sign study-specific informed consent and authorization for the release of their protected health information prior to registration. Patients must be registered in the prior to treatment with study drug.

2.1.1.13 Women of childbearing potential must have a negative β-HCG pregnancy test documented within 14 days prior to registration.

2.1.1.14 Women of childbearing potential and male participants must practice adequate contraception.

2.1.1.15 All patients must have an LVEF measurement of at least 50% by Echo or MUGA (if clinically indicated) within 14 days prior to registration. The method used for LVEF assessment in an individual subject must be the same throughout the trial

2.1.2 Exclusion Criteria

2.1.2.1 Prior invasive malignancy that is not the ependymoma (except non-melanomatous skin cancer or carcinoma in situ of the cervix) unless the patient has been disease free and off therapy for that disease for a minimum of 3 years.

2.1.2.2 Severe, active comorbidity, defined as follows:

- Transmural myocardial infarction or unstable angina within 3 months prior to study registration
- Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days prior to registration
- New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration
- History of stroke or transient ischemic attack within 3 months prior to registration.
- Inadequately controlled hypertension (systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg despite antihypertensive medication)
- History of cerebral vascular accident (CVA) within 3 months prior to registration.
- Serious and inadequately controlled cardiac arrhythmia
- Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection)
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

2.1.2.3 Patients cannot be receiving HAART (Highly Active Anti-Retroviral Therapy) therapy.

2.1.2.4 Pregnant or nursing women because of concern of fetal/infant exposure to these

agents.

2.1.2.5 Any condition that impairs ability to swallow pills (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, active peptic ulcer disease).

2.1.2.6 Patients cannot be receiving EIAEDs nor any other CYP3A4 inducers such as rifampin or St. John's wort beginning at least 14 days prior to registration Step 2. A reference list of prohibited drugs is provided in Appendix 16.3.

2.1.2.7 Patients cannot be receiving CYP3A4 inhibitors beginning at least 7 days prior to registration Step 2. A reference list of prohibited drugs is provided in Appendix 16.3.

2.1.2.8 Patients must not have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment).

2.2 PRETREATMENT EVALUATION

2.2.1 Baseline testing and evaluations that do not impact eligibility

2.2.1.1 Baseline MDASI-SP or MDASI-BT questionnaire (Appendix **12.7** or **12.8**).

2.2.1.2 Total protein, albumin, calcium, phosphorus, glucose, BUN, uric acid, alkaline phosphatase, LDH, and when appropriate, anticonvulsant levels will be performed prior to initiation of treatment.

2.2.1.3 PT, PTT and INR (obtained only on patients receiving warfarin therapy).

2.2.2 Baseline testing and evaluations that do impact eligibility.

2.2.2.1 H&P to include prior therapy for the current cancer, blood pressure, Concurrent Medications, KPS and Neurologic examination within 14 days prior to registration.

2.2.2.2 Brain or spine MRI within 14 days prior to registration. Patient must be on a steroid dose that has been stable or decreasing for at least 5 days. If the steroid dose is increased between the date of imaging and registration, a new baseline MRI is required.

2.2.2.3 **NOTE:** Residual disease following resection of recurrent tumor is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, an MRI should be done no later than 96 hours in the immediate postoperative period or at least 4 weeks postoperatively, within 14 days prior to registration. If the "within 96-hour of surgery" scan is more than 14 days before registration, the scan needs to be repeated

2.2.2.4 Baseline Cardiac Testing to be performed within 14 days prior to registration includes:

- EKG.
- Echo or MUGA scan (MUGA preference as clinically indicated). These studies must be performed under the supervision of an experienced cardiologist, presumably at the same high-volume laboratory for the duration of the trial. The method used for LVEF assessment in an individual subject must be the same

throughout the trial. The guidelines of the American Society of Echocardiography will be used. These guidelines can be located on the www at http://www.asecho.org/Guidelines.php.

2.2.2.5 Baseline Laboratory examinations to be conducted within 14 days prior to registration include:

- CBC with Differential and Platelets.
- Chemistries to include: SGPT (ALT), bilirubin, serum creatinine.
- Serum Pregnancy Test: Beta-HCG in women with childbearing potential.

2.3 REGISTRATION PROCEDURES

This protocol is no longer open to accrual or registration.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a phase II study to determine the efficacy of the combination of temozolomide and lapatinib in recurrent brain ependymoma and anaplastic ependymoma as measured by median progression-free survival**.** Eligible patients will receive 2 cycles of the combination of temozolomide and lapatinib. The temozolomide will be administered at a dose of 125 mg/m2 as a single daily dose on days 1-7 and 15-21 of a 28-day cycle. The lapatinib will be given as a single daily dose of 1250 mg orally. Patients who do not experience any grade 1 or greater myelotoxicity will be eligible to have the temozolomide dose increased to 150 mg/m^2 as a single daily dose on days 1-7 and 15-21 of a 28-day cycle. The lapatinib dose will not be increased.

Patients who exhibit response to protocol therapy and have not experienced any significant or intolerable toxicities may continue to receive protocol therapy up to a maximum number of 24 cycles. Patients that are showing sustained Complete Response (CR), Partial Response (PR) or Stable Disease (SD) may continue Post protocol single agent therapy with lapatinib. Post-protocol lapatinib supply may be obtained through Glaxo Smith-Kline (GSK). Patients on post protocol single agent lapatinib will have follow up visits every 2 months for survival assessment and radiographic evaluation of disease per MRI or CT scan.

3.2 DRUG ADMINISTRATION

3.2.1 The first and second cycle will consist of the combination of temozolomide and lapatinib. The temozolomide will be administered at a dose of 125 mg/m2 as a single daily dose on days 1-7 and 15-21 of a 28-day cycle. The lapatinib will be given as a single daily dose of 1250 mg orally.

3.2.2 Cycle 3 and beyond. The dose of temozolomide for cycle 3 and subsequent treatment cycles will depend upon the tolerance of the first 2 cycles. Patients who do not experience any grade 1 or greater myelotoxicity (white blood cell count, absolute neutrophil count or platelet count) will be eligible to have the temozolomide dose increased to 150 mg/m^2 as a single daily dose on days 1-7 and 15-21 of a 28-day cycle. The lapatinib dose will not be increased.

3.2.2.1 The dose will be determined using the body surface area (BSA) calculated at the beginning of each odd treatment cycle unless significant (> 3 kg) weight loss or gain is observed. The BSA will be calculated from the height obtained at the pretreatment visit and from the weight obtained at the visit before each odd cycle. Capsules of temozolomide are available in 5, 20, 100, 140, 180 and 250 mg. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

3.2.2.2 Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). The start of the first cycle will be scheduled within 7 days of registration. The start of all subsequent cycles (2-24) will be scheduled every 4 weeks (28 $\pm$ 3 days) after the first daily dose of temozolomide of the preceding cycle.

3.2.2.3 Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration, and 1 hour before or 1 hour after lapatinib administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

3.2.2.4 Antiemetic prophylaxis with a 5-HT_3 antagonist is strongly recommended and should administered 30 to 60 minutes before temozolomide administration

3.3 DOSE MODIFICATION

3.3.1 Lapatinib

3.3.1.1 First Cycle**:** Lapatinib will be started at 1250 mg once a day as continuous oral dosing. There is no dose escalation from the starting dose.

Dose Level	Dose Schedule once a day	Remarks
- 2	750 mg	Reduction if prior AE
-1	1000 mg	Reduction if prior AE
0	1250 mg	Starting dose

3.3.1.2 Summary of dose modifications

Dermatologic		
Rash – acne/acneiform • Intolerable Grade 2 & Grades 3-4		Hold dose. • Re-evaluate at least weekly until AE resolved to ≤ 1 or tolerable Grade 2. • Re-treat at a one dose level reduction • If AE persists > 4 weeks, remove patient from study Patients with Grade 4 AEs related to agent should be taken off study. Note: Grade 2 lapatinib related rash may not automatically require dose reduction. However, for Grade≥ 3 rash or recurrent intolerable Grade 2 rash, reduce 1 dose level.
Gastrointestinal		
Diarrhea • Grade 1 • Grade 2 • Grade 3, 4 or intolerable Grade 2:		No intervention required Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs until diarrhea free for 12 hrs) • Hold dose. • Loperamide, hold agent until recovery to ≤ Grade 1 and then reduce 1 dose level • If AE persists > 4 weeks, remove patient from study • Patients with Grade 4 AEs related to agent may be taken off study at investigator's discretion.
Ocular/Visual		
Keratitis • Grade 1		• Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks[1]. • Dose reduction not required.

• Grade 2 or 3		• Manage as for Grade 1 keratitis[1]. • Grade 2 persistent (>14 days) or Grade 3: Hold dose. Re-treat at a reduced dose after resolution or amelioration of AE to ≤ Grade 1 at the discretion of the investigator. • Persistent Grades 2 or 3: Remove patient from study for persistent Grade ≥2 keratitis after dose held for 14 days. Ophthalmologic F/U should be scheduled at a frequency determined by the ophthalmologist
Pulmonary/Upper Respiratory		
Signs and symptoms of Interstitial Pneumonitis		Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated. Hold dose pending diagnosis Permanently discontinue lapatinib if diagnosis is confirmed and considered possibly related to lapatinib.
All other non-hematologic adverse events		
Any Grade 2 of concern (*e.g.*, prolonged cardiac,		Hold dose. • Re-treat at a reduced dose after resolution or amelioration of AE to ≤ Grade 1 If AE persists > 4 weeks , remove patient from study
Grade 3 or 4		Hold dose. • Re-evaluate until AE resolved to ≤ Grade 1 (or tolerable Grade 2). • If AE persists >4 weeks, remove patient from study • Patients with Grade 4 AEs related to agent may be taken off study at investigator's discretion.

3.3.1.3 Liver Chemistry Stopping and Follow-up Criteria

3.3.1.3.1 Liver Chemistry Stopping Criteria

3.3.1.3.1.1 Liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology. All subjects who meet liver chemistry criteria requiring permanent discontinuation of lapatinib must continue to be followed for the study assessments and procedures as defined in Section 3.7.6and Appendix 12.5If a subject experiences ALT >3 × ULN and total bilirubin >2.0 × ULN (>35% direct; bilirubin fractionation required*), then the following actions must be taken:

- immediately and permanently discontinue investigational product;
- complete the SAE data collection tool, and the clinical evaluation CRF;
- in addition to the liver event follow up assessments defined below, the following are suggested: specialist or hepatology consultation; anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies; and liver imaging and/or liver biopsy to evaluate liver disease;
- promptly report the event to NCI CCR within 24 hours of learning of its occurrence (refer to Section 7.4);
- monitor every week until liver chemistries resolve, stabilize or return to within baseline values;
- do not re-challenge with lapatinib.
- **NOTE**: bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >2.0 × ULN, then the aforementioned actions must still be performed.

3.3.1.3.1.2 If a subject experiences:

- ALT >8 × ULN or
- ALT >5 × ULN persisting for ≥2 weeks: retest within 3 days from the first occurrence and then weekly to determine if ALT elevation persists or
- ALT >3 × ULN with signs or symptoms of hepatitis or hypersensitivity (the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia),
- Total Bilirubin > 2 x ULN in absence of Gilbert's Syndrome

then hold investigational product for 2 weeks, repeat liver chemistry testing in 2 weeks, and then call the Study Chair (Dr. Mark Gilbert) to discuss the possibility of re-challenging with investigational product.

3.3.1.3.1.3 If the treatment is exhibiting efficacy **and** the subject wants to continue for potential benefit of lapatinib therapy after being informed of the results of liver chemistry testing, then the lapatinib may be re-started at the reduced dose agreed upon by the investigator and the Study Chair. The liver event CRF should be completed and liver chemistries and aforementioned signs and symptoms should

be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol.

3.3.1.3.1.4 If a subject experiences ALT >3 × ULN but <5 × ULN and total bilirubin ≤2 × ULN, without signs or symptoms of hepatitis or hypersensitivity, **and** who can be monitored weekly, then the following actions should be taken:

- continue investigational product;
- monitor weekly until liver chemistries resolve, stabilize, or return to within baseline, then monitor liver chemistries as per protocol assessment schedule;
- if ALT >3 and < 5 × ULN for > 4 weeks , discontinue the treatment;
- if at any time this subject meets any of the aforementioned liver chemistry stopping criteria, then proceed as described above.

3.3.1.3.2 Liver Chemistry Follow up Criteria

3.3.1.3.2.1 For all subjects who meet any of the liver chemistry criteria described above, make every attempt to carry out the liver follow up assessments described below:

- Viral hepatitis serology including:
    - Hepatitis A IgM antibody;
    - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
    - Hepatitis C RNA;
    - Cytomegalovirus IgM antibody;
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
    - Hepatitis E IgM antibody (if subject resides or has travelled outside USA or Canada in past 3 months);
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Complete blood count with differential to assess eosinophilia;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form;
- Record alcohol use on the liver clinical evaluation case report form.
- Refer to Appendix **12.5** for a liver safety algorithm detailing stopping and follow up criteria.

3.3.1.4 Cardiac Assessments

3.3.1.4.1 Cardiac Definitions

3.3.1.4.1.1 Cardiac Death is defined as either:

- Cardiac death due to heart failure, myocardial infarction, or arrhythmia.
- Probable cardiac death defined as sudden, unexpected death within 24 hours of a definite or probable cardiac event.

3.3.1.4.1.2 Severe symptomatic CHF is defined as New York Heart Association (NYHA) Class III or IV (Class III defined as being not capable of climbing one flight of stairs and class IV defined as having symptoms at rest) and a drop in LVEF of more than 10 points from the baseline and to below 50%. In these cases there is *no need* to perform a confirmatory second LVEF assessment. The method used for the LVEF assessment must be the same method as used for the baseline assessment.

3.3.1.4.1.3 Asymptomatic (NYHA I) or mildly symptomatic (NYHA II) is defined as a significant drop in LVEF, confirmed by a second LVEF assessment within approximately three weeks showing also a significant drop in LVEF. A significant drop is defined as an absolute decrease of more than 10 points below the baseline LVEF and to below 50%. The method used for LVEF assessment must be the same method used for the first (baseline) assessment.

New York Heart Association Functional Classification

I	No Symptoms and no limitations in ordinary physical activity.
II	Mild Symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable at rest.
IV	Severe limitations. Experiences symptoms even while at rest.

3.3.1.4.1.4 Stopping and holding rules

- Stopping rule

Treatment with any of the treatment regimens defined for this study will be permanently stopped if a patient develops a symptomatic cardiac event or an asymptomatic event confirmed by repeat evaluation. However, patients will remain in the study and all efforts will be made to complete all assessments as planned.

- Treatment

It is strongly recommended that patients who have symptomatic decreases in LVEF or those who meet the criteria for stopping treatment seek cardiologic consultation for advice on potential treatment for their cardiac dysfunction.

3.3.2 Temozolomide

3.3.2.1 Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

Dose Level	Dose mg/m^2	Remarks
- 2	75	Reduction if prior AE
-1	100	Reduction if prior AE
0	125	Starting dose for cycle 1and 2, increase to 150 mg/m^2 for cycle 3 and beyond if non hematologic toxicity ≤ grade 2 and hematologic toxicity ≤ grade 1
+1	150	Highest possible dose level

3.3.2.1.1 First and Second Cycle: Temozolomide will be started at a dose of 125mg/m^2/day.

3.3.2.1.2 Third Cycle: The dose of temozolomide will be determined according to: (1) treatment related non-hematologic AE during the preceding treatment cycle, as well as (2) the worst ANC and platelet counts.

3.3.2.1.3 Delay: On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and all grade 2, 3 or 4 non-hematologic AEs (except for alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).

3.3.2.1.4 If AEs persists, treatment should be delayed by 1 week for up to 4 consecutive weeks. If, after 4 weeks of delay, all treatment related AEs have still not resolved (to grade ≤ 1): then any further treatment with temozolomide should be stopped.

3.3.2.1.5 Dose Escalations and Reductions: If, during the first and second cycle, all hematologic AEs observed were ≤ grade 1 and treatment related non-hematologic AEs observed were grade ≤ 2 (except alopecia, lymphopenia, nausea and vomiting) then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycles 1and 2 temozolomide has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 3, then the dose should not be escalated in further cycles (4-24).

3.3.2.1.5.1 Dose reductions: If any treatment related non-hematologic AE observed was grade > 2 (except alopecia, lymphopenia, nausea and vomiting) and/or if platelets < 50 x 10^9/L and/or ANC < 1 x 10^9/L, then the dose should be reduced by one dose level. Patients who require more than two dose reductions will have treatment stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, lymphopenia, nausea and vomiting) then temozolomide treatment should be stopped.

3.3.2.1.5.2 Subsequent cycles (4-24*):* Any dose reductions of temozolomide will be determined according to: (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the lowest ANC and platelets observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied. *Important:* If the dose was reduced or delayed for AEs, there will be no dose re-escalation in subsequent treatment cycles.

3.3.2.2 Summary of Dose Modifications or Discontinuation for Temozolomide-Related Adverse Events

Worst Treatment-Related Non-Hematologic AE (except for alopecia, nausea, and vomiting) During the Previous Cycles	
Grade	**Dose Modification**
0-2	No dose modifications for non-hematologic AEs. Dose reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except alopecia, nausea, and vomiting).
4	Stop (except alopecia, nausea, and vomiting). Dose modifications based on ANC and platelet counts are not applicable.

3.3.2.3 Worst Treatment-Related Hematologic AE During the Previous Cycle

Worst AE		**Platelets**		
		≥100 x 10^9/L	**50 – 99 x 10^9/L**	**< 50 x 10^9/L**
ANC	**≥ 1.5 x 10^9/L**	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	≥1 & <1.5 x 10^9/L	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	< 1 x 10^9/L	Reduce by 1 dose level	Reduce by 1 dose level	Reduce by 1 dose level

Note: A complete blood count must be performed on days 14 and 28 (± 72 hours) after the first daily dose of each treatment cycle.

Hematologic AE on Day 1 of Each Cycle (within the prior 72 hours before Day 1)	
AE	**Delay**
ANC< 1.5 x 10^9/L and/or Platelet count < 100 x 10^9/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematologic AE (except for alopecia, nausea, and vomiting) On Day 1 of Each Cycle (within the prior 72 hours)	
Grade	**Delay**

2-4	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AE, then no escalation is possible.

3.3.3 Instructions on Missed Dose

- Patients should be instructed to take the medication as soon as it is remembered.
- The next due dose should be taken no sooner than 12 hours after the previous dose, and the time of administration of the subsequent doses should be adjusted until it is back on its regular "am or pm" schedule.

3.4 LENGTH OF PROTOCOL THERAPY

3.4.1 Patients who exhibit response to protocol therapy and have not experienced any significant or intolerable toxicities may continue to receive protocol therapy up to a maximum number of 24 cycles.

3.4.2 Patients who have exhibited objective response or clinical benefit at 12 months/cycles of study agents will have the option of stopping protocol treatment at this time at the discretion of their treating physician.

3.4.3 Similarly**,** treating physicians will also have the option of re-starting protocol therapy on patients that had tumor recurrence after study treatment was stopped after 12 months/cycles, with the stipulation that protocol therapy is not beyond 24 months from start of treatment date.

3.5 QUESTIONNAIRES

The MDASI-BT or SP (Appendix **12.7** or 12.8) will be utilized for this portion of the study. Full instruments are provided in the appendix. In addition, information regarding demographics and treatment history will be collected as part of the larger study and used in this analysis.

The MDASI-BT or SP consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, those associated with increased intracranial pressure, and those related to focal deficits. The questionnaire also includes ratings of how much symptoms interfered with different aspects of a patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0 - 10 scales. The average time to complete these instruments is 5 minutes. The MDASI-BT or SP has been translated into 18 languages [17, 20].

3.6 STUDY CALENDAR

STUDIES TO BE OBTAINED	Pre-Study (within 14 days of study registration)	Course 1 and 2 (± 3 days)	Courses 3-24 (± 3 days)	Discontinuation - Completion of Therapy, and/or Post Protocol Therapy
Consent & HIPAA Authorization	X[9]			
History	X			
Physical Exam (Ht, Wt, BSA, VS)	X	X[1]	X[1]	X
KPS Performance Status	X	X[1]	X[1]	X
Neurologic Exam	X	X[1]	X[1]	X
CBC, differential, platelets	X	X[2], X[10]	X[2]	X
PT, PTT, INR[7]	X	X[2], X[10]	X[2]	X[7]
Serum Pregnancy Test (β-HCG)	X			
Total Protein, Albumin, Ca++, PO_4, Glucose, BUN, Serum Creatinine, Uric Acid, Alkaline Phosphatase, LDH	X	X[3], X[10]	X[3]	X
SGPT (ALT), Total Bilirubin	X	X[3]	X[3]	X
Echocardiogram or MUGA	X		X[1]	X
EKG[8]	X			
MRI head and/or spine with gadolinium	X		X[1]	X[4], X[11]
MDASI Symptom Assessment	X		X[1,6]	X
Collect Treatment Diary and perform Pill Counts			X[1]	X
Patient status assessment				X[5], X[11]

[1] Every 8 weeks (except for Ht).
[2] Every 2 weeks.
[3] Every 4 weeks.
[4] For patients with stable disease or response, MRI surveillance should continue every *2 months for 1 year* after treatment completion, then every 3 months for 1 year, then every 4 months for 1 year, then every 6 months until progressive disease, lost to follow-up or death. For patients who develops progressive disease while on follow-up under the "off treatment follow-up schedule", reference section 3.7.9 for instructions.
[5] Patients removed from the study for disease progression or treatment-related toxicity should continue to be followed with quarterly updates of treatment regimens, disease status and survival.
[6] To be completed within +/- 1week of the MRI assessment date.

[7] Only for patients receiving warfarin and performed at baseline, bi-monthly for the duration of protocol therapy, at discontinuation of lapatinib and a minimum of (1 more lab draw) 2 weeks following discontinuation of lapatinib.
[8] EKG will be performed at baseline, and as clinically indicated during the study
[9] To be obtained at pre- study. Timing for obtaining consent is not limited to "within 14 days of study registration".
[10] Labs (chemistry, coagulation and hematology) does not have to be repeated prior to Cycle 1 as long as it is obtained within 14 days of start of treatment date.
[11]Patients on post protocol lapatinib must have follow-up visit and MRI or CT scan every 2 months.

3.7 ON STUDY EVALUATION

3.7.1 Physical Exam to include, Vital Signs, a neurologic examination, and KPS Performance status, will be performed every 8 weeks prior to initiation of every other cycle of therapy (i.e prior to cycle 3, cycle 5, cycle 7 etc.) and when therapy is discontinued. Patient treatment diaries will be collected and pill counts will be performed prior to every other cycle of therapy and when therapy is discontinued.

3.7.2 Total protein, albumin, calcium, phosphorus, glucose, BUN, creatinine, uric acid, alkaline phosphatase, LDH, and when appropriate, anticonvulsant levels will be performed prior to initiation of treatment and before each course of therapy.

3.7.3 MRIs will be done before every other course of treatment (prior to cycle 3, 5, 7. etc.).

3.7.4 MDASI-BT and/or SP at the time of clinical evaluation with MRI as long as the clinical therapy is being administered (Appendix 12.7 or 12.8.

3.7.5 A CBC with differential and platelets will be obtained every 2 weeks.

3.7.6 Hepatic Monitoring: SGPT (ALT), total bilirubin levels will be performed:

- During treatment phase: every 4 weeks, prior to each course of therapy, for the duration of chemotherapy administration (or more frequently, if clinically indicated)
- During post-treatment phase: continue to monitor any liver chemistry abnormalities noted during treatment or within 30 days after last dose of lapatinib until values return to normal or baseline
- bilirubin fractionation (when testing is available) is recommended if total bilirubin >2 x ULN
- See section 3.7.6 and Appendix 12.5 for Liver Chemistry Stopping and Follow-up criteria in the presence of abnormal LFT results.

3.7.7 Cardiac Monitoring:

- LVEF will be assessed every 8 weeks (2 cycles) by Echo or MUGA (MUGA preference as clinically indicated) scan. The method of evaluation used for the

LVEF assessment in an individual subject must be the same method used at baseline and throughout the duration of the trial.

- Echo or MUGA (if clinically indicated) studies must be performed under the supervision of an experienced cardiologist, presumably at the same high-volume laboratory for the duration of the trial. The guidelines of the American Society of Echocardiography will be used. These guidelines can be located on the www at http://www.asecho.org/Guidelines.php
- Subsequent scheduled LVEF assessments must be performed as per Appendix 12.6, "LVEF Assessment Algorithm".
- In addition, any subject who develops clinical signs and symptoms of cardiac failure should undergo an LVEF assessment and ECG.

3.7.8 After enrollment on the clinical trial, patients will complete as baseline measures the MDASI-BT or MDASI-SP. The patient will continue to complete the MDASI-BT and/or MDASI-SP at the time of clinical evaluation with MRI as long as the clinical therapy is being administered, unless clinical deterioration makes self-report not possible before that time. The time when patients are unable to complete the self report questionnaires will be used as part of the study analysis. The MDASI-BT and/or MDASI-SP will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self report.

3.7.9 Off treatment follow-up will continue on the following schedule until the patient meets off study criteria.

3.7.9.1 For patients with stable disease or response, MRI surveillance should continue every 2 months for 1 year after treatment completion, then every 3 months for 1 year, then every 4 months for 1 year, then every 6 months until progressive disease is noted, death or lost to follow-up.

3.7.9.2 Patients removed from study treatment for disease progression or treatment-related toxicity should continue to be followed with quarterly (every 3 month) updates of treatment regimens, disease status and survival.

3.7.9.3 Stable disease (SD) patients who develops progression while being followed on the "off treatment follow-up schedule", will continue with follow-up requirements on the PD off treatment follow-up schedule, until patient meets off study criteria.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.8.1 Criteria for Removal from Protocol Therapy

A genuine effort must be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the trial. Information regarding the reason for not completing the trial will be recorded on the appropriate case report forms.

It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued the reason will be recorded on the appropriate case report form. Reasons that a patient may discontinue participation in a clinical study are listed below:

Any patient who receives at least one dose of trial medication will be included in the safety analysis.

3.8.1.1 Evidence of recurrent or progressive disease

3.8.1.2 Second malignancy

3.8.1.3 Development of unacceptable toxicity during treatment

3.8.1.4 Non-adherence to the protocol

3.8.1.5 Refusal of therapy

3.8.1.6 Pregnancy

3.8.1.7 At 2 years of protocol therapy

3.8.2 Off Study Criteria

3.8.2.1 Death

3.8.2.2 Lost to follow-up

3.8.2.3 Withdrawal of consent for continued follow-up

3.8.2.4 Protocol defined follow-up completed

3.8.2.5 Withdrawal of consent

3.8.3 Off study procedure

For participating CERN sites:
When a subject is taken off-study, notify CCR study coordinator via encrypted email. (Christine Bryla email: christine.bryla@nih.gov)

3.8.4 POST PROTOCOL THERAPY AND FOLLOW UP

3.8.4.1 Post Protocol Single Agent Lapatinib

Patients that are showing sustained Complete Response (CR), Partial Response (PR) or Stable Disease (SD) may continue Post protocol single agent therapy with lapatinib. Post protocol lapatinib supply may be obtained through Glaxo Smith-Kline (GSK), using the same drug ordering mechanism as detailed in section 10.2.12 (Agent Ordering/Requests).

3.8.4.2 Post Protocol Follow Up

Patients on post protocol single agent lapatinib will have follow up visits every 2 months for survival assessment and radiographic evaluation of disease per MRI or CT scan.

3.9 SURGICAL THERAPY

Not applicable in this protocol

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 SUPPORTIVE CARE

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

4.1.1 Anticonvulsants*:* Antiepileptic medications should be used as indicated. However, only patients taking non-hepatic enzyme inducing antiepileptic drugs (non-EIAEDs) or no antiepileptic drugs are eligible to enroll on this trial. Patients must not be taking EIAEDs for at least 2 weeks prior to registration. See Appendix 12.2for a list of EIAEDs and non-EIAEDs.

During therapy, patients who were previously on a non-EIAED and need to change anticonvulsants should be started on another non-EIAED if at all possible. No delays in treatment would be required.

If patients who were previously on no anticonvulsants require initiation of an anticonvulsant, a non-EIAED should be used if at all possible.

If a patient is started on an EIAED while on the study, he/she should immediately be started on another non-EIAED and the EIAED should be tapered and discontinued as quickly as possible. The patient may continue the lapatinib. The dates that the patient took an EIAED should be noted.

Patients who need to permanently change anticonvulsants but who cannot change to another non-EIAED will be taken off study.

4.1.2 Analgesics*:* As needed.

4.1.3 Hematopoietic Growth factors: Permitted for grade 4 neutropenia or neutropenia with fever and should follow American Society of Clinical Oncology guidelines for their use.[*] Prophylactic use of growth factors is not allowed, nor can they be used to improve blood counts to allow initiation of treatment.

4.1.4 Treatment of rash: The acneiform rash associated with lapatinib treatment appears to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with any of the following: minocycline topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, and oral prednisone (short course). Minocycline recommended dose: 200 mg po bid (loading dose), followed by 100 mg po bid for 7-10 days.

4.1.5 Nutritional Supplementation: Permitted.

4.1.6 Antacids: Permitted.

4.1.7 Calcium Supplements: Calcium supplements (e.g., calcium carbonate, 500 mg PO three times daily) may be required to maintain serum calcium levels above the lower limit of normal during chemotherapy treatment. Vitamin D supplements (e.g., ergocalciferol, 400 IU PO daily) may be appropriate for persistent hypocalcemia.

4.1.8 Anti-emetics/Anti-diarrheals: The nausea, vomiting, and diarrhea that may occur with lapatinib or temozolomide administration can generally be managed through the use of appropriate supportive measures [anti-emetics (e.g., 5-HT_3 antagonists, benzodiazepines, prochlorperazine) and antidiarrheal medications (e.g., loperamide)]. Specific guidelines for the use of loperamide for the subacute (days after administration) form of irinotecan-induced diarrhea are provided below:

- Patients should not be given drugs with laxative properties.
- Loperamide should be started at the earliest sign of: (1) a loose stool, or (2) the occurrence of 1-2 more bowel movements than usual in 1 day, or (3) a significant increase in stool volume or liquidity. Loperamide should be taken in the following manner:
    - 4 mg at the onset of diarrhea and then 2 mg by mouth every 2 hours, around the clock until the patient is diarrhea free for at least 12 hours. Patients may take loperamide every 4 hours during the night.
- Patients should increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

5 BIOSPECIMEN COLLECTION

5.1 PATHOLOGY REVIEW

5.1.1 General Information

Tissue evaluation is mandatory for this study. The evaluation will consist of confirmation that the histologic features meet WHO criteria for ependymoma, as well as an analysis of molecular markers MGMT methylation status. All blocks for review will be sent directly to Dr. Aldape.

5.1.2 Rationale

The purpose of analyzing the tissue samples is to confirm the diagnosis of ependymoma, as well as to determine the status of key molecular markers. As described below, such markers will be examined in an effort to further characterize other factors that may be predictive of response and prognosis using the treatment regimens that are undergoing evaluation in this clinical trial. Furthermore, in the case where frozen tumor tissue is also available, more extensive genetic testing will be performed so that correlative profiles of gene expression to response and outcome can be made in this carefully studied, uniformly treated group of patients.

5.1.3 Specimen Collection*:* Tissue specimens should be taken from pre-study diagnostic open biopsy or surgical resection.

5.1.3.1 To be eligible for this study, the patient must have an ependymoma. Features of a grade II or III ependymoma according to WHO guidelines must be present.

5.1.3.2 The following materials will be required for tissue evaluation:

5.1.3.2.1 Representative tissue blocks that contain diagnostic tumor. As a guide, at least 1 cubic centimeter of tissue composed primarily of tumor is desired. If tissue block is not available, 15 unstained slides from a representative tumor block is required.

5.1.3.2.2 If a representative tissue block is submitted, an accompanying H&E is encouraged for rapid diagnosis but not required. If an H&E is included, Dr. Aldape will use this for the review. If not included, Dr. Aldape will cut a section from the paraffin block, stain this with H&E, and use that slide for the review.

5.1.3.2.3 A Pathology Report documenting that the submitted material contains tumor; the report must include the protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

5.1.3.2.4 Tissue evaluation will be required for every case before study registration Step 2. Send pathology material by overnight mail directly to:

Ken Aldape, MD
MacFeeters- Hamilton Centre for Neuro-Oncology,
101 College St, Room 14-701
Princess Margaret Cancer Centre,
Toronto Medical Discovery Tower (TMDT),
Toronto, ON M5G 1L7
Canada
kaldape@gmail.com

5.1.3.2.5 Include on the tissue submission form the name, telephone number, and fax number of the person to notify with the results of the tissue evaluation.

5.1.3.2.6 Shipments must be made Monday through Thursday.

5.1.3.2.7 Notify Dr. Aldape by email on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.

5.1.3.2.8 Dr. Aldape will email the appropriate contact person from the submitting institution with the results and will send the completed form to the institution electronically.

5.1.3.2.9 If the patient does not meet eligibility requirements, *all* tissue and forms will be returned to the participating submitting institution.

5.1.3.2.10 If a tissue block is provided, after confirming histopathologic diagnosis Dr. Aldape will cut sections for molecular analysis.

5.2 LABORATORY CORRELATES

Relative to other gliomas, little is known regarding the relevant molecular lesions in ependymoma that contribute to the biologic and clinical behavior of these neoplasms. Activation of the EGFR pathway, as stated above, has been described. In addition, while MGMT methylation has been reported at low frequency, too few cases have been evaluated to lead to firm conclusions. Finally, activation of the PI3K-AKT pathway has not been fully characterized, and its evaluation is justified based on the central role of this pathway in human tumors. Accordingly, molecular testing will include an evaluation of these pathways as well as genome wide screens. Tumor tissue will be evaluated immunohistochemically for expression of EGFR. Activation of the PI3K/AKT pathway will be determined by immunohistochemistry for p-AKT, p-mTOR as well as p-S6. MGMT methylation will be determined using real-time PCR of DNA following bisulfite treatment. Since little is known regarding molecular lesions in ependymoma, genome-wide screens will be performed and will include microarray expression profiling using the Illumina DASL assay (unpublished data from our laboratory suggest that this is feasible in formalin-fixed paraffin embedded tissue). Data from the Cancer Genome Atlas indicate that methylation profiling in glioblastoma is likely to lead to clinically useful biomarkers. Accordingly, methylation profiling using the Illumina Golden Gate Cancer panel, will be performed on these ependymoma samples. These screens as well as the targeted molecular assays will provide the basis for a future molecular classification of ependymoma based on site of origin as well as clinical factors (grade and patient outcome).

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be collected/reported in a secure research database. The PI will be responsible for overseeing entry of data and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Sites will enter data on paper Case Report Forms; then transfer study data to NCI via fax, mail or Secure E-mail and File Transfer Service (SEFT). Contracted Data Managers will enter the data into a secure research database.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.1.1 Confidentiality

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e., Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the NCI must have the patient's full name & social security number "blacked out" and the assigned patient ID number, protocol accession number, and protocol number written in. Patient initials may be included or retained for cross verification of identification.

6.1.2 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study has obtained a Certificate of Confidentiality, which helps to protect personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality.

6.1.3 Safety Data

All patients receiving study agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, CNS observations, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. All toxicities encountered during the study will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded prior to each course of therapy. Life-threatening toxicities that are unexpected and assessed to be possibly related to the study agent/s should be reported immediately to the study Coordinator and Institutional Review Board (IRB).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring

after starting study drug (or therapy) even if the event is not considered to be related to study drug.

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

6.2 RESPONSE CRITERIA

6.2.1 The primary endpoint is median progression-free survival. A combination of the neurological examination and MRI brain scan will be used to define progression. Due to improvements in neuroimaging and the fact that tumor growth in certain regions of the CNS is without immediate neurologic signs and symptoms, greater reliance is placed on neuroimaging to define progression.

6.2.2 Definitions of Response

6.2.2.1 Measurable Disease: Bi-dimensionally measurable lesions with clearly defined margins by MRI scan.

6.2.2.2 Objective Status, To Be Recorded at Each Evaluation**:** If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

6.2.3 Response Criteria

6.2.3.1 Stable/No Progression**:** No evidence of new measurable lesions on MR imaging. The designation of Stable/No Progression requires a minimum of 12 weeks duration. All measurable and evaluable sites must be assessed using the same techniques as baseline.

6.2.3.2 Partial response: ≥ 50% reduction in the sum of products of all measurable lesions over baseline sum observed using the same techniques as baseline, The patient must be on a stable or decreased dose of corticosteroids to be evaluable for response.

6.2.3.3 Complete response: Complete resolution of all lesions. The patient cannot be on any corticosteroids with the exception of adrenal replacement doses.

6.2.3.4 Progression: 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

6.2.3.5 Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

6.2.4 Neurologic Function Score: This method of neurologic evaluation notes the presence or absence of neurologic symptoms. This examination should coincide with objective measurement in tumor size.

0	No neurologic symptoms
1	Minor neurologic symptoms
2	Moderate neurologic symptoms – fully active
3	Moderate neurologic symptoms – less than fully active
4	Severe neurologic symptoms

6.2.5 Performance Status: Patients will be graded according to Karnofsky Performance Status (KPS)

6.2.6 Time to Treatment Failure: From date of registration to the date of first observation of progressive disease, non-reversible neurologic progression or permanently increased steroid requirement (applies to stable disease only), death due to any cause, or early discontinuation of treatment.

6.2.7 Survival: From date of registration to date of death due to any cause

6.2.8 **NOTE: Steroids**: Steroid dosage will be carefully monitored and recorded during each course of therapy and steroid dosage changes will be considered before response determinations are made.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 PROTOCOL SPECIFIC DEFINITIONS

7.1.1 Events *not* considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event *not* fulfilling any of the definitions of serious given above and *not* resulting in hospital admission.
- Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.
- Liver function abnormalities meeting pre-defined stopping criteria (See section 3.7.6 & Appendix 12.5) will be reported promptly to NCI once the investigator determines that the event meets the protocol definition for that event

7.1.2 In addition to reporting the SAEs described below, the following protocol specific reporting criteria will be reported:

- All Grade 4 laboratory abnormalities.

- Cardiovascular events have been seen in subjects taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines and interstitial pneumonitis has been reported in subjects taking compounds that inhibit ErbB1. As a precaution, the following will be reported as SAE:
- Cardiac dysfunction will be reported as an SAE and will be defined as any signs or symptoms of deterioration in left ventricular cardiac function that are ≥Grade 3 (NCI CTCAE) or a ≥20% decrease in LVEF relative to baseline, which is also, below the institution's LLN. Refer to NCI CTCAE grading of left ventricular cardiac function.
- Any signs or symptoms of pneumonitis that are ≥Grade 3 (NCI CTCAE) (defined as radiographic changes and requiring oxygen). Refer to NCI CTCAE grading of pneumonitis/pulmonary infiltrates.
- Hepatobiliary events have been seen in subjects taking lapatinib and other tyrosine kinase inhibitors. As a precaution, the following will be reported as an SAE:
- ALT >3 × ULN and total bilirubin >2.0 × ULN (>35% direct; bilirubin fractionation required).
- **NOTE**: bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >2.0 × ULN, then the event should still be reported as an SAE. Other hepatic events should be documented as an AE or an SAE as appropriate.

7.2 GENERAL DEFINITIONS

7.2.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per section 7.4

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention

- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.2.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.2.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.2.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

7.2.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.2.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.2.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.2.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.2.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 ASSESSING CAUSALITY

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

Yes: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

7.4 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.4.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NIH-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations

- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.4.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

7.5 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

Participating centers must also submit the report to their IRB in accordance with their institutional policies. The CCR problem report form will be used for this purpose (Appendix **12.9**).

Occasionally NCI IRB or the PI may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

7.6 REPORTING TO THE STUDY DRUG MANUFACTURERS

The NCI Coordinating Center will forward all SAE reports to the NCI IRB and GSK Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

GSK Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

FAX: 610-917-6715

SAEs will be forwarded to GSK Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E) **in accordance with the following:**

All serious adverse events should be reported to GSK Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E) within 24 hours. In the event of an SAE, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures. In brief:

The Investigator/Sponsor may report serious adverse drug reactions (SADRs) using either:
An ADEERS form (Adverse Event Expedited Reporting System) available at http://ctep.cancer.gov/reporting/adeers.html

OR

A MedWatch form available at http://www.fda.gov/medwatch/

Occasionally the coordinating center may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

7.7 GUIDELINES & PROCEDURES FOR REPORTING VIOLATIONS, DEVIATIONS AND UNANTICIPATED PROBLEMS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." The definition is often left to the Lead Institution IRB. Accordingly, since NCI, Center for Cancer Research is the Coordinating Center and the Protocol Chair must adhere to those policies set by the NCI IRB, the definitions for unanticipated problem and protocol deviation as described by the NCI IRB will be applied for reporting purposes for all institutions participating in the NCI Center for Cancer Research Multi-center Project. Definitions are listed in section **7.2**

Protocol Deviations or Unanticipated problems occurring at a participating institution will be submitted to that institution's own IRB in accordance with local policies and procedures. However, the participating institution must submit a report to the NCI CCR Coordinating Center even in instances where the local IRB does not require a report.

Deviations or Unanticipated problems must be submitted to the NCI CCR Coordinating Center within 7 calendar days after the original submission to the IRB, or after becoming aware of the event (if not reportable to the local IRB), or upon receipt of notification from the NCI CCR Coordinating Center. When Deviations or Unanticipated Problems are reported to NCI CCR, but, the local IRB does not require a report, the report that is submitted to the NCI CCR Coordinating Center must be accompanied by a formal memo explaining the local policy and the rationale for not reporting the event to the local IRB.

Deviation or Unanticipated problem Reports and any accompanying documentation (to include the local IRB acknowledgement of the event when applicable) are to be submitted to the NCI CCR Coordinating Center using the problem report form in section **12.9.**

NCI Center for Cancer Research Coordinating Center: Upon receipt of the deviation/unanticipated problem report from the participating institution, the NCI CCR

Coordinating Center will submit the report to the lead Protocol Chair for review. Subsequently, the participating institution's IRB deviation/unanticipated problem report will be submitted to the NCI IRB for review.

7.8 DATA AND SAFETY MONITORING PLAN

7.8.1 Principal Investigator/Research Team

The clinical research team will have a teleconference every other week when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.8.2 NCI Coordinating Center Monitoring Plan

Data will be reviewed by the study coordinator at the NCI Center for Cancer Research, who will check for missing data, non-compliance, and adverse events. Missing data will be requested from participating sites. The study coordinator and PI meet weekly and discuss the data as needed. The PI and study coordinator will ensure that all non-compliance and unanticipated problems are reported to the NCI IRB in accordance with reporting requirements.

8 STATISTICAL CONSIDERATIONS

The primary goal of this trial will be to assess time to progression, defined as progressive disease, toxicity at a level of severity that precludes the patient continuing on the protocol, or death. Patients will be accrued up to a maximum sample size of 50. Safety monitoring of failure time will be done as follows. Every 2 months, the data from each patient will consist of the time to failure. We define T_i to be the Time to Progression for the *i* th patient parameterized via a median parameter such that $T_i \mid Q_E \sim Exp(Q_E)$ and $Median(T_i) = Q_E$. We assume that Q_E has prior distribution $Inverse\ Gamma(a_E, b_E)$ with expectation $b_E / (a_E - 1)$. Thus, for each treatment the posterior distribution of $Q_E \mid Data$ is $Inverse\ Gamma(a_E + m_E, b_E + \ln(2)\sum T_i)$ (where m_E is the number of events in the trial). *A priori*, it is assumed that the median PFS time Q_E follows an inverse gamma distribution with shape parameter= 2 and scale parameter =17.6761. This prior distribution has median of 10.5 months. The historical median PFS time is represented by Q_S. In addition, Q_S is assumed to follow an inverse gamma distribution with shape parameter= 2000 and scale parameter =21000. (This prior also has median of 10.5 months).

The trial will be stopped early if, based on the current data, Pr ($Q_E > Q_S + 3.5$| data) < 0.065. That is, the trial will be stopped early if, it is very unlikely that the median time to progression with the experimental therapy (temozolomide and lapatinib) is less than the historical median time to progression for the standard treatment as described in the literature. The rule will be applied every 2 months, with the probability criterion recomputed based on the most recent data available at that time. Based on an anticipated accrual rate of 2.5 patients per month, the trial is expected to complete accrual in 40 months.

To obtain operating characteristics of the early stopping rule, the trial was simulated under three scenarios, which we have summarized in the Table below. The design's operating characteristics are as follows. Each entry in the table is the mean from 2000 simulated trials:

Table Operating Characteristics. Maximum sample size 50

Case	Median Time to Progression	Pr(Stop Early)	# Patients (25%,75%)
Scenario 1	2.0	1	16.435 (13, 19)
Scenario 2	7.0	0.896	36.694 (27, 50)
Scenario 3	10.5	0.173	47.354 (50, 50)
Scenario 4	14.0	0.034	49.054 (50, 50)

We also summarize the median lower and median upper credible intervals for this trial on an assumption of that the data follows an exponential distribution (with median survivals summarized in the Table below). To calculate the expected lower and expected upper credible intervals we simulated progression free survival data (1000 simulations) from exponentially distributed data and assuming observations without events were censored at 48 months (40 months of accrual and 8 months of additional follow-up). For each simulation we recorded the lower (1st decile) and upper (9th decile) credible sets from the posterior distribution of the median PFS parameter. At the end of the simulation we then calculated and recorded below the median 1st decile and median 9th deciles from the vector of recorded deciles obtained from our simulation.

True Median Survival	Median 1st decile and Median 9th decile Credible Limits
10.5 Months	(8.72, 12.50)
14 Months	(11.52, 16.66)

Secondary Efficacy Analysis

The secondary endpoint of this trial is anti-tumor activity as determined by the overall response (CR or PR) rate. MacDonald criteria will be used to determine the overall response. Patients must have completed at least 4 weeks of treatment to be considered evaluable for overall response, unless treatment is stopped for neurologic progression. Patients with neurologic progression will be scored as non-responders regardless of duration of treatment.

Safety Analysis

All patients will be considered evaluable for safety after the first dose of therapy. AEs and clinically significant laboratory abnormalities with associated incidence rates and severities will be tabulated.

Deaths and Serious Adverse Events

Serious adverse events and deaths will be listed. Data from the adverse event page that specify the event is serious will be used to generate the listing.

Summaries of serious unique adverse events will include:

- all serious treatment emergent adverse events,
- all serious treatment emergent adverse events by sex,
- all serious treatment emergent adverse events by race,
- all serious treatment emergent adverse events by the worst grade,
- all related serious treatment emergent adverse events by the worst grade.

Neurological Symptoms and Signs

Neurological symptoms and signs collected on the neurological examination CRFs will be summarized at the baseline and by scheduled visit.

Laboratory Tests

Changes from baseline in laboratory measurements will be summarized by study visit.

The worst post-baseline laboratory measurements up to (1) 30 days after the permanent discontinuation of the study medication or (2) the initiation of subsequent anti-ependymoma therapy will be summarized. Marked laboratory toxicity (baseline grade 0 to post-baseline grade 3 or 4, or baseline grade 1 to post-baseline grade 4) will also be summarized.

Vital Signs, Weight and Karnofsky Performance Status

Descriptive statistics will be used to summarize vital signs, weight, and Karnofsky performance status. For continuous outcomes the mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be reported for change from baseline at each scheduled visit. For discrete (i.e., Karnofsky performance status) outcomes, descriptive analyses will be based on the distribution of this outcome and will be reported as percentages and patient counts by category.

MDASI-BT

The sample size for this trial was based on the primary end point of the study.

Received MDASI-BT and MDASI-SP forms will be checked versus the timing schedule and considered as valid if they fall within one week of the scheduled assessment. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point.

We will use descriptive statistics to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. The proportion of patients rating their symptoms to be 7 or

greater (on a 0-10 scale) will also be reported. We will construct individual patient profiles for each of the selected symptoms to describe the individual patients' patterns of change over time. We will calculate the mean core symptom severity, mean severity of the MDASI-BT or MDASI-SP and mean symptom interference at the time of clinical evaluation. Estimates of differences in the mean symptom severity and mean symptom interference between responders and non-responders will be estimated in the intent to treat population. All patients with at least one valid questionnaire, BT and/or SP, will be included in the analyses. Questionnaires completed at study registration will be considered baseline. All questionnaire data received after randomization will be used in the primary analyses.

Differences of at least 2 points will be classified as the minimum clinically meaningful change in the symptom severity and symptom interference measures. For example, an increase of 2 points or more would mean a moderate improvement, whereas a decrease of 2 points or more would be interpreted as moderate worsening. For individual symptoms, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate. Ependymomas occur in patients of all races and although there is a slight predominance in men, this is a disease that is also common in women. The molecular targets of the Temozolomide and Lapatinib within the tumor are not known to be different among patients based on gender or race; hence this study will be open to all adults.

9.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because of unknown toxicities of the study agents in the pediatric patient. Furthermore, the targets of the Temozolomide and Lapatinib are not as prevalent in pediatric malignant ependymomas and therefore, the efficacy of this regimen will be initially determined in the adult population before consideration of its use in pediatrics.

9.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The primary risk to patients participating in this research study is from the toxicity of Temozolomide and Lapatinib, or both drugs. Both are investigational agents in the treatment of ependymoma. The protocol provides for detailed and careful monitoring of all patients to assess for toxicity. Toxicity data from the current dose level will be collected and reviewed to ensure that there were no severe toxicities that would preclude further patient enrollment. Patients will be treated with therapeutic intent and response to the therapy will be closely monitored.

9.4 RISKS/BENEFITS ANALYSIS

9.4.1 Benefits

The potential benefit to a patient on this study is a reduction in the bulk of their tumor and improvement in cancer lesions, which may or may not have favorable impact on symptoms and/or survival.

9.4.2 Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

9.4.3 Risks/Benefits Analysis

The potential benefits from this therapy are disease stabilization or shrinkage and a reduction in symptoms caused by the brain tumor such as neurological deficits and headache. Given the efforts to minimize risk with the administration of this combination, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual subjects.

9.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed. The informed consent process will be documented in the patient's medical record and on the informed consent document. This process will be performed by the local Principal Investigator or designee.
If new safety information results in significant changes in the risk/ benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, be given a copy of the revised form, and be asked give their consent to continue in the study.

10 PHARMACEUTICAL INFORMATION

There will be no IND obtained for the use of lapatinib in this study.
This study meets the criteria for exemption for an IND as this investigation is not intended to support a new indication for use or any other significant change to the labeling;
the drugs are already approved and marketed and the investigation is not intended to support a significant change in advertising; and the investigation does not involve a route of administration or dosage level in use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

10.1 TEMOZOLOMIDE AGENT INFORMATION (TEMODAR)

Please refer to the package insert for comprehensive information.

10.1.1 Formulation

10.1.2 Other Names: - methazolastone; Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 180 mg and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF.

10.1.3 Mode of Action: Alkylating agent of imidazotetrazinone class.

10.1.4 Storage and Stability

The capsules are packaged in 30 cc, 28 mm, 48 Type I amber glass bottles (30 capsules/bottle) and should be stored at 25°C but temperatures between 15 and 30 degrees centigrade are permissible. Capsules are stable for at least 30 months when stored in amber glass bottles at this temperature.

10.1.5 Supply: Commercially available

10.1.6 Pharmacokinetics

Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

10.1.7 Metabolism and Elimination

*T*emozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

10.1.8 Special Populations

10.1.8.1 Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m^2). Caution should be exercised when temozolomide is administered to

patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

10.1.8.2 Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

10.1.8.3 Gender: Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

10.1.8.4 Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of grade 4 neutropenia and grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

10.1.8.5 Drug-Drug Interactions: In a multiple dose study, administration of temozolomide with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

10.1.9 Known Potential Adverse Events

Hematologic: Thrombocytopenia, leukopenia, myelodysplastic syndrome

Gastrointestinal: Nausea, vomiting, anorexia

Hepatic: Elevated liver enzymes (reversible)

Skin: Rash

Neurologic: Convulsions, weakness on one side of the body, abnormal coordination, paralysis

Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

Likely (occurring in more than 20% of patients)

- fatigue
- alopecia
- constipation
- headache
- nausea
- anorexia
- seizures
- vomiting

Common (occurring in 3-20% of patients)

- dizziness
- abnormal muscle movements/ coordination
- abnormal gait
- hemiplegia or partial paralysis
- upper and/or lower extremity edema
- weakness (such as weakness on one side of the body)
- tickling/tingling sensation
- pain (such as in the abdomen, joints, back, and/or muscles)
- breast pain in females
- confusion
- memory problems
- anxiety
- depression
- difficulty sleeping
- drowsiness
- skin rash
- pruritus
- dry skin
- mucositis
- dysphagia
- dysgeusia or taste changes
- diarrhea
- excess steroid in the body (possible bruising and/or increase in size of the face and/or neck)
- viral infection
- weight gain
- loss of urinary control
- urinary tract infection
- frequent urination
- abnormal vision
- blurry vision
- diplopia or double vision
- fever
- head cold
- cough
- sore throat
- sinusitis
- dyspnea
- allergic reaction

Temozolomide may commonly cause low blood cell counts (white blood cells, red blood cells, and platelets). This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion.

Rare but serious (occurring in fewer than 3% of patients)

- bone marrow disease where not enough blood cells are made
- hallucinations
- nervous system disease (possible pain and/or weakness)
- neuropathies (nerve damage- possible numbness, tingling, and pain)
- hyperglycemia (possible diabetes)
- hypokalemia (possible weakness)
- severe allergic reaction
- new occurrence of cancer (including myeloid leukemia)
- allergic skin reaction
- severe skin damage with loss of a large portion of skin
- weight loss
- fever due to low white blood cell counts
- bruising
- hemorrhage
- Steven-Johnson Syndrome
- damage from radiation (such as skin damage)
- pneumonitis (lung inflammation)
- flu-like symptoms
- injection site reactions (skin redness, irritation, pain, itching, swelling, and/or warmth)
- opportunistic infection
- herpes infection causing painful skin rash (shingles)

The following side effects have been reported in research studies with temozolomide. It is unclear if these side effects were caused by temozolomide, but they may be:

- BUN blood level increase
- creatinine blood elevated
- lymphopenia
- thrombocytopenia
- neutropenia
- death
- hypoxia
- weight loss
- epistaxis
- sepsis
- cholecystitis
- pancreatitis
- GI perforation
- dehydration

10.1.10 Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered**.**

10.1.11 Contraindications: Temozolomide is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

10.1.12 Pregnancy Category D

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.**

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are

being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

10.2 LAPATINIB (NSC#727989)

10.2.1 Chemical Name:

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

10.2.2 Molecular Formula:

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

10.2.3 Molecular Weight:

943.48

10.2.4 Other Names:

Lapatinib, Tykerb™

10.2.5 Mode of Action

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

10.2.6 How Supplied

Lapatinib is supplied by GlaxoSmithKline 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 150 tablets per container.

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

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

10.2.7 Storage

The intact bottles should be stored at controlled room temperature (15°C-30°C) and protected from light.

10.2.8 Stability

Shelf life surveillance studies of the intact bottle are on-going. Current data indicates Lapatinib is stable for at least 2 years at controlled room temperature (15°C - 30°C).

10.2.9 Route of Administration

Oral on an empty stomach (either 1 hour before or 1 hour after meals).

10.2.10 Method of Administration:

Whenever possible, whole tablets should be administered. lapatinib tablets have not been

deliberately formulated to be dispersible tablets; however, in circumstances where dosing of whole tablets is not possible, such as patients being unable to swallow or being fed through nasogastric tubes, tablets may be administered as a dispersion in water. Liquids other than water should not be used. Care should be taken to ensure that the whole dose is administered.

10.2.11 Supplier

Lapatinib is supplied to investigators by GlaxoSmithKline (GSK).

The lapatinib supplied for this study will be commercial grade lapatinib labeled for commercial use. Each pharmacy must re-label the bottles for investigational use.

10.2.12 Agent Ordering

All regulatory document requirements prior to requesting study agents. GlaxoSmithKline (GSK) requires a copy of each Principal Investigator's CV and Medical license to be forwarded to GSK. This information will be forwarded to GSK by the NCI upon protocol activation for each site. After this is done lapatinib may be requested directly from GlaxoSmithKline by the Principal Investigator (or their authorized designees) at each participating institution. NCI policy requires that the agent be shipped directly to the institution where the patient is to be treated. NCI does not permit the transfer of agents between institutions.

Requests for drug supply should be sent to Mary Jo Penna at:

Mary Jo Penna
North America Medical Affairs, GSK Oncology
1250 S. College Rd., UP4440
Collegeville, PA 19426-0989
E-mail: mary-jo.q.penna@gsk.com
Telephone: 610-917-5109

10.2.13 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.

10.2.14 Investigational Drug Disposition Policy

Investigational Agent Destruction or Returns

Investigators/Designees should make every effort to minimize the amount of agent ordered and returned or destroyed unused, (e.g. limit inventories to an 8 week supply or less). Investigators/Designees must return or destroy unused supplied agent as directed by the protocol when:

- The agent is no longer required because the study is completed.
- Agent is outdated. Investigators/designees should only return or destroy outdated agents with a firm expiration date or if they have received written notification that an agent has expired and should be returned or destroyed.
- The agent is damaged or unfit for use. Investigators/designees should contact the supplier prior to returning or destroying investigational agents because of stability concerns, (e.g. loss of refrigeration or exposure to elevated temperatures). Do **NOT**

return broken vials. Broken vials should be destroyed at the clinical site. Follow the appropriate agent accountability guidelines.

The destruction of the study agent should be carried out in accordance with the local institutions policies and procedures. The destruction of the agent must be documented on the DARF.

10.2.15 Drug Interactions

In vitro studies with human liver microsomes indicate that CYP3A4 and CYP3A5, and to a lesser extent CYP2C19, may be the enzymes primarily responsible for Lapatinib metabolism.

Therefore, compounds known to modulate CYP3A4 activity may therefore affect metabolism of Lapatinib. Inhibitors of CYP3A4 may decrease the metabolism and increase Lapatinib levels, while inducers of CYP3A4 may increase the metabolism and decrease Lapatinib levels. Ketoconazole, a CYP3A4 inhibitor, has been shown to elevate Lapatinib plasma concentrations 3.5-fold. Carbamazepine, a CYP3A4 inducer, has been shown to reduce Lapatinib plasma concentrations by 72%. Therefore, co-administration of Lapatinib with known inhibitors or inducers of CYP3A4 should be avoided. If there is no medically acceptable alternative coadministration should proceed with caution.

There may be a potential interaction between Lapatinib and warfarin. Patients have experienced elevated INRs and bleeding with warfarin and quinazolines. Patients on warfarin and Lapatinib should have more frequent INR/PT determinations after starting Lapatinib (e.g. weekly for the first month and weekly for a minimum of 2 weeks following discontinuation of Lapatinib. Alternatively, to avoid this interaction, it is strongly advised to switch patients to low molecular weight heparin, e.g. 5000 units of deltaparin subQ daily, or Lovenox 40mg sub Q daily.

In addition, Lapatinib may inhibit CYP3A4 and increase concentrations of drugs metabolized by CYP3A4.

Glucocorticoids: should be used at lowest effective dose of dexamethasone. Note that dexamethasone equivalent dose > 1.5 mg/day, may alter metabolism of Lapatinib (see chart below for conversion). Glucocorticoid Conversion Table

Glucocorticoid	Equivalent Dose (mg)
Cortisone	25
Hydrocortisone	20
Prednisone	5
Methylprednisolone	4
Dexamethasone	0.75

In human in vitro systems, Lapatinib showed minimal induction potential of CYP3A activity and was shown to have varying inhibitory potential towards CYPs 3A4, 1A2, 2C9, 2C19, and 2D6 at concentrations above those observed clinically in human plasma.

Gastric pH Modifiers may modify the absorption of lapatinib. Therefore, the administration of H2 inhibitors, proton pump inhibitors should be noted on the CRF. Antacids should not be given within 1 hour before and after dosing with Lapatinib.

One should attempt to maximize the time interval between Lapatinib and proton pump inhibitors (aim for a 12hr interval if possible) Schedule Lapatinib at least one hr prior to the PPI or H2 blocker. It may help to take Lapatinib with a coke or pepsi drink.

See Appendix 18.6 for a partial list of medications that induce or inhibit CYP3A4.

10.2.16 Lapatinib Prohibited Medication List

10.2.16.1 Inhibitors of CYP3A4

The following drugs are prohibited beginning at least seven (7) days prior to registration Step 2 and for the duration of the study:

- Antibiotics: clarithromycin, erythromycin, troleandomycin, telithromycin, ciprofloxacin, norfloxacin
- Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole (doses up to 150 mg/day are permitted)
- Antidepressants: nefazodone, fluvoxamine
- Calcium channel blockers: verapamil, diltiazem
- GI: cimetidine, aprepitant
- Miscellaneous: Grapefruit or its juice, amiodarone*; Bitter Orange
- *Amiodarone use should have been discontinued at least 6 months prior to the administration of the first dose of study medication and for the duration of the study.

10.2.16.2 Inducers of CYP3A4

The following drugs are prohibited beginning at least fourteen (14) days prior to registration Step 2 and for the duration of the study.

- Anticonvulsants: phenytoin, carbamezepine, Barbiturates (e.g. Phenobarbital), oxcarbazepine
- Antibiotics: all rifampin class agents (e.g. rifampin (rifampicin), rifabutin, rifapentene)
- Miscellaneous: St. John's Wort, modafinil

10.2.16.3 Gastric pH Modifiers (not to be administered within 1 hour before and after Lapatinib dosing)

- H2 blockers (ranitidine, nizatidine, famotidine), proton pump inhibitors(omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole), antacids

10.2.17 Pre-clinical Toxicology

A range of toxicology studies has been conducted to support the oral administration of Lapatinib to humans. Repeat oral dose toxicity studies have been completed in rats and dogs for up to 6 and 9 months, respectively. The effects of Lapatinib on fertility in the rat and embryofetal development in the rat and rabbit have been investigated. A range of genetic toxicity studies has been performed in vitro and in vivo. The significant findings from the toxicology studies are summarized below.

Following single oral administration, Lapatinib was well-tolerated by both CD-1 mice and Wistar Han rats at doses up to 2000 mg/kg. Treatment-related findings consisted of reversible changes in

body weight and body weight gain as well as reversible GI effects.

A 13-week oral dose ranging pilot carcinogenicity study in mice showed that treatment with Lapatinib at doses up to 200 mg/kg/day was generally well tolerated. Microscopic changes attributable to treatment with Lapatinib were noted in the liver and preputial gland of males and large intestines (cecum and colon) of males and females.

Administration of Lapatinib to rats and dogs for up to 6 months or 9 months resulted primarily in exaggerated pharmacologic effects and organ toxicities generally associated with degenerative and/or inflammatory epithelial changes (GI tract and accessory digestive organs, skin, mammary gland, liver and prostate). Other treatment-related effects included clinical signs, decreased body weight and food consumption, organ weight changes and alterations in clinical pathology parameters. Following the recovery period, treatment-related changes were either significantly improved or completely reversed.

There were no effects on male or female rat gonadal function, mating, fertility or pregnancy nor were there any increases in the number or incidence of any malformations when rats or rabbits were given Lapatinib during the period of major organogenesis. At maternally toxic doses (≥60 mg/kg/day in rats and rabbits), Lapatinib treatment was associated with growth retardation and developmental variations.

In genetic toxicity studies, Lapatinib was demonstrated to be non-mutagenic and nonclastogenic.

Lapatinib was well tolerated in dogs at doses of <40 mg/kg/day (treated for 39 weeks). The No Observed Adverse Effect Level (NOAEL) in dogs was 10 mg/kg/day for both males and females. Inflammatory gastrointestinal toxicities were noted on repeated dosing along with changes in the epithelium of tissues that were considered related to EGFR inhibition. Fertility studies in male and female rats demonstrated no Lapatinib-related effects at any dose tested. No fetal malformations occurred when Lapatinib was given to pregnant, female rats or rabbits during the period of major organogenesis (Investigator's Brochure, 2003). At maternally toxic doses (60 mg/kg/day in rats and rabbits), Lapatinib treatment was associated with growth retardation and developmental variations.

Groups of 4 male and 4 female beagle dogs treated orally with Lapatinib at 10, 40, or 160 mg/kg/day for up to 93 days resulted in mild leukocytosis (females only), mild decreases in albumin, total protein, and calcium, and mild increases in globulin, cholesterol, ALT, alkaline phosphatase, total bilirubin and total bile acids. Improvement occurred in all parameters during the 29-day recovery period (Investigator's Brochure, 2003).

An additional study evaluated Lapatinib administered orally daily to groups of 4 male and female Beagle dogs at 0, 10, 40, or 100 mg/kg/day for 39 weeks. The effects noted on the skin of males given 100-mg/kg/day and females given >40 mg/kg/day included ulceration with epidermal hyperplasia or epidermal hyperplasia with inflammation and follicular atrophy (Investigator's Brochure, 2003).

Lung alveolar histiocytosis and/or interstitial inflammation were seen in the 14-day and 3-month rat study and in the 3-month dog study. This was seen at doses ≥180 mg/kg/day in rats and at 160 mg/kg/day in dogs. No lung changes were seen when Lapatinib was given chronically for 6 or 9 months at lower doses (Investigator's Brochure, 2003).

Cardiac changes were seen at a low incidence (3 males and 1 female) only at the high dose in the rat 3-month study. The lesions in the heart were identical to those observed with a spontaneous

age-related cardiomyopathy primarily seen in male Wistar rats. In spite of a 7 fold greater exposure in female rats, the incidence was consistent with the natural history of this spontaneous lesion. There were no cardiac changes in the rat 6-month study or in all dog studies indicating that Lapatinib is not directly cardiotoxic (Investigator's Brochure, 2003).

10.2.18 Clinical Studies and Toxicities

As of November 2003, four trials in healthy volunteers had been completed, and five Phase 1 studies and four Phase 2 studies in cancer patients were ongoing. A phase 1 study of Lapatinib at doses of 175 to 1800 mg/day in heavily pre-treated patients (n=39) with solid tumors reported that the drug was well-tolerated and showed preliminary evidence of antitumor activity. In this study, 3 patients in each of the 175 and 375 mg/day cohorts; 4 in the 675, 900, and 1600 mg/day cohorts; 6 in the 1200 mg/day and 9 in the 1800 mg/d were enrolled. Six additional patients were administered 900 mg bid to compare safety of bid versus qday schedules. Grade 1-2 rash, diarrhea, nausea, vomiting, constipation, fatigue, and anorexia were the most frequent adverse events in all qday dose cohorts. Grade 3 toxicity was not observed in any of the qday dose cohorts. Grade 3 diarrhea was observed in 2 of 6 patients at 900 mg bid, requiring dose reductions. Eight patients (non-small cell lung cancer (NSCLC), carcinoma of unknown primary site, head and neck, colon, breast carcinomas) remained on study with stable disease (SD) of 4+ months duration. Two NSCLC patients resistant to gefitinib (ZD1839, Iressa™) had minor responses (MRs) (3+ months, 12 months). Patients continuing on therapy for more than 4 months had received Lapatinib at doses > 1200 mg/day. Lapatinib was well tolerated when administered on a qday schedule, with preliminary evidence of anti-tumor activity in this heavily pre-treated population (Burris, Hurwitz et al. 2005).

A Phase 1B trial evaluating tolerability and effects on biomarkers in tumor biopsies in heavily pre-treated patients with metastatic disease expressing EGFR or erbB2 reported that Lapatinib was well tolerated at all dose levels tested (500-1600 mg/day)(Burris, Hurwitz et al. 2005). Of 33 evaluable patients, 3 partial responses (PR) (10%) and 12 SD (36%) were reported. An evaluation of tumor biopsies obtained prior to, and after 2-3 weeks of treatment with Lapatinib revealed that induction of apoptosis in tumor tissue and inhibition of intratumor expression of activated Erk1/2, Akt and cyclin D protein appeared to correlate with PR and SD (Burris, Hurwitz et al. 2005). Disease progression was associated with persistent, high levels of expression of these biomarkers. Treatment with Lapatinib was not effective when insulin growth factor receptor (IGFR) was highly expressed (Bacus, Gudkov et al. 2000). Tumor types in which objective response or stable disease were seen included: breast (7), colorectal (2), ovarian (2), lung (1), granular cell (1), and head and neck (1) carcinomas as well as adenocarcinoma of unknown primary (1). Objective responses were observed in ErbB2-expressing breast cancer patients who had progressed after receiving prior trastuzumab (Herceptin™)-based regimens. The most common adverse events included grade 1-2 rash (25%), diarrhea (27%), and nausea/vomiting (21%).

10.2.19 Reported Adverse Events and Potential Risks

Common Adverse Effects:

- Constitutional Symptoms: fatigue (lethargy, malaise, asthenia), insomnia
- Dermatology/Skin: rash (acne/acneiform), rash (desquamation)
- Gastrointestinal: diarrhea, anorexia, nausea, vomiting

Less Common Adverse Effects:

- Constitutional Symptoms: weight loss
- Dermatology/Skin: flushing,
- Gastrointestinal: distension/bloating (abdominal), heartburn/dyspepsia, mucositis/stomatitis (clinical exam) - oral cavity, constipation, early satiety
- Pain: head/headache
- Syndromes: flu-like syndrome
- Cardiac arrhythmia: atrial fibrillation
- Pulmonary/Upper respiratory: pneumonitis/pulmonary infiltrates

Uncommon Adverse Effects:

- Blood/Bone Marrow: hemoglobin, platelets*
- Constitutional Symptoms: fever, weight loss
- Cardiac General: left ventricular systolic dysfunction, hypotension
- Dermatology/Skin: pruritus
- Gastrointestinal: dehydration, taste alteration, flatulence
- Lymphatics: edema: limb
- Metabolic/Laboratory: bilirubin*, AST*, ALT*
- Neurology: neurology - other*
- Ocular/Visual: blurred vision
- Pain: abdomen NOS
- Sudden Death
- HepatoBiliary: Liver dysfunction/failure (clinical)

* These events were only reported in studies of Lapatinib in normal volunteers, a few of whom received a placebo.

Also reported on Lapatinib trials but with the relationship to Lapatinib still undetermined:

- leukocytes (total WBC)

10.2.20 Recommended management for most common toxicities:

Rash: Skin rash (usually grade 1-2) has been observed during the first several days of treatment with EGFR inhibitors and has been observed to diminish in severity after 4 weeks of treatment in many patients. In some patients, this rash appeared to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with several agents. In patients with severe rash, treatment may need to be discontinued or the dose reduced. Anecdotal reports of improvement have occurred with any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course).

Diarrhea: Diarrhea has been seen with Lapatinib and with other EGFR inhibitors. In general EGFR inhibitor-induced diarrhea has been transient, usually not of sufficient severity to hinder administration of the agents, and responsive to loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg q 2-4 hr until diarrhea free for 12 hr.

Nausea: Routine premedication for nausea is not necessary, but symptomatic patients should be treated with standard anti-nausea/antiemetic therapy as necessary.

If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

10.2.21 Safety Issues

Due to the limited amount of experience in human subjects, there is only preliminary information available about the relationship of adverse events and administration of Lapatinib. The following adverse events are included in the development core safety information for Lapatinib: diarrhea, which may lead to dehydration, nausea, fatigue, rash (including dermatitis acneiform), vomiting and anorexia. At present, there are no known absolute contraindications with Lapatinib, with the exception of individuals who are hypersensitive to this compound.

Congestive heart failure has been reported in the clinic with trastuzumab (Herceptin™), a monoclonal antibody directed against the ErbB2 receptor. This cardiomyopathy has been seen at a higher incidence in patients that previously received anthracyclines and is characterized by dilatation and thinning of the ventricular walls with decreased left ventricular ejection fraction. As of 21 January 2004, a total of 10 patients in Phase I and II studies of Lapatinib have experienced a decrease in LVEF, 9 of which showed decreases ≥ 20% from baseline LVEF.

In Phase I trials, 2 patients reported asymptomatic Grade 2 decreases in LVEF, and neither event met the criteria of an SAE. For one patient (study EGF10003), the etiology of the LVEF decrease remains indeterminate, and a drug-related effect cannot be excluded. The LVEF decrease in the other patient (study EGF10004) was not assessed as drug related, the patient having a prior history of cardiac disease. Both patients withdrew from treatment because of progressive disease.

A total of eight serious adverse event reports of decreased LVEF were received for patients participating in Phase II studies. After the first two serious adverse events and possibly related cases, GSK instituted a 'per protocol' serious criterion of LVEF decreases ≥20% from baseline and below the institutions' lower limit of normal. For all eight cases the investigators considered there was a reasonable possibility that the LVEF decreases were associated with Lapatinib. Two patients presented with symptoms (breathlessness and signs of cardiac failure) and were found as part of their examination to have LVEF reduction. Both patients had co-morbidities, which could have contributed to the symptoms (pericardial and pleural effusions in one; diabetes, coronary artery disease, hypertension and hypercholesterolaemia in the other). The remaining six Phase II reports were asymptomatic and discovered during the routine protocol specified cardiac monitoring. These events were reported as serious per the protocol specific requirement. Treatment with Lapatinib was stopped in all eight Phase II patients and the LVEF decrease resolved with the exception of one patient who died of disease progression before a follow-up assessment was completed. Because of the known effects of trastuzumab on cardiac function and the observed transient reductions of LVEF seen among patients receiving Lapatinib, only patients with normal LVEF are eligible for study and patients will undergo monitoring of LVEF while on this study.

Interstitial pneumonitis/lung disease has been reported with the structurally similar anilinoquinazoline, gefitinib (ZD1839, Iressa™), which inhibits EGFR tyrosine kinase. The incidence and death rate has been reported to be 0.44% and 0.12% respectively world wide and 1-2% and 0.4-0.5% respectively in Japan. At the time of the SAE data cut off, 30 January 2004, no cases of idiopathic interstitial pneumonitis (IP) has been reported in phase I monotherapy. However, one patient in study EGF10004 was diagnosed with interstitial pneumonia which the investigator attributed this event to disease under study and not related to Lapatinib. Two reports of possible interstitial pneumonitis in studies of Lapatinib have been received, both occurring in the phase I combination study with the FOLFIRI regimen (EGF10011). One report was considered possibly related to treatment with Lapatinib and one is unknown. Both patients reported in this study were asymptomatic, had pulmonary metastases, and were diagnosed with interstitial pneumonitis after undergoing routine CT scanning for disease assessment. Both cases resolved. One report of possible interstitial pneumonitis has been reported from Phase II study EGF20002. The event reported was an SAE of pulmonary pneumonitis and was ongoing at the time of the reporting. Treatment was interrupted and the investigator considered the event unrelated to Lapatinib and related to disease under study, pericardial effusion and treatment failure. Lapatinib should be withheld pending investigation and diagnosis in patients with symptoms and signs of suggestive pneumonitis. Patients diagnosed with pneumonitis possibly related to Lapatinib should be removed from study.

Fetal malformations were not observed when Lapatinib was administered to pregnant female rats or rabbits during the period of major organogenesis. At maternally toxic doses, Lapatinib treatment was associated with growth retardation and developmental variations. There has been no evidence of genotoxicity or clastogenicity in mutagenic studies. In healthy volunteers (EGF10013) receiving the CYP3A4 inhibitor ketoconazole at 200 mg twice daily for 7 days, plasma concentrations (AUC) of Lapatinib were increased approximately 3.5-fold, and half-life increased 1.7-fold. In healthy volunteers (EGF10018) receiving the CYP3A4 inducer carbamazepine (CBZ) at 100 mg twice daily for 3 days and 200 mg twice daily for 17 days, plasma concentrations (AUC) of Lapatinib were decreased approximately 72%.

These results are consistent with the strong dependence of Lapatinib elimination on CYP3A metabolism. Co-administration of Lapatinib with known inhibitors or inducers of CYP3A4 should proceed with caution. The most common toxic effects of Lapatinib are diarrhea, which may lead to dehydration, nausea, fatigue, rash (including dermatitis acneiform), vomiting and anorexia.

Co-administration of Lapatinib with known inhibitors of CYP3A4, and/or compounds metabolized by CYP3A4, should proceed with caution. In vitro studies have shown that Lapatinib is metabolized predominantly by CYP3A4 and CYP3A5, and to a lesser extent by CYP2C19. Lapatinib has also been shown to have inhibitory potential towards CYP3A4 Investigator's Brochure, 2003). At this time, the effect of known inhibitors of CYP3A4 on Lapatinib metabolism or the effect of Lapatinib on drugs metabolized by CYP3A4 is unknown.

As part of ongoing pharmacovigilance by GlaxoSmithKline, a review of all hepatobiliary events reported across the entire lapatinib clinical development programme has been performed. Two hundred sixteen reports of hepatic events were retrieved from the GSK safety database as of 31 December 2007 regardless of source (clinical trials, spontaneous/marketed use data). In 39 of the 216 cases, a causal association to lapatinib could not be ruled out: 38.5% (15/39) of these subjects received lapatinib monotherapy, 53.8% (21/39) of subjects received lapatinib in combination with

other chemotherapies, such as capecitabine, and 3 cases were still blinded.

A total of 13 deaths were identified which contained hepatobiliary events. In 3 of these cases, an association with lapatinib could not be excluded. The remaining 10 cases were confounded by the patients underlying condition (progressive disease and/or progression of pre-existing liver metastases).

Based on an additional sub-analysis, of 18 clinical studies of lapatinib in breast cancer, using Hy's Law (defined as AST or ALT >3 x ULN, and total bilirubin >2 x ULN, with no initial findings of cholestasis i.e.: ALP <2 x ULN) as a predictor for potential drug induced liver injury, the liver injury associated with lapatinib seems to be the result of a prolonged exposure to the drug. All the subjects whose events potentially met Hy's Law received study medication for three months or longer. The majority of these cases appeared reversible. Most patients experienced a decline in liver enzymes with drug cessation.

Based on the results of this review, GSK concluded a causal relationship between hepatobiliary disorders (specifically transaminase elevations) and lapatinib cannot be excluded. As a consequence, hepatotoxicity was added to the core safety information (CSI) for lapatinib. In addition, for ongoing clinical trials, the monitoring interval for hepatic function has been increased to every 4-6 weeks during treatment, and stopping rules have been added for severe hepatic events. Lapatinib dosing should be discontinued if changes in liver function are severe and patients should not be retreated.

10.2.22Pharmacokinetics

Pharmacokinetic studies in healthy subjects receiving daily doses of Lapatinib (10-250 mg) found that the agent was well tolerated and resulted in moderate accumulation in systemic exposure (Bence, Anderson et al. 2005). Peak concentrations (C_{max}) occurred 3-4 hours following drug administration. Drug accumulation of at least 50% was reported over an 8-day dosing period based on trough concentrations. AUC values increased with increasing dose in a nearly proportional manner. The average half life ($t_{1/2}$) was 8 hours.

The pharmacokinetics of Lapatinib are similar in healthy volunteers and patients, demonstrating oral absorption that is incomplete, highly variable, and sometimes delayed. After dosing, plasma concentrations rise to a peak at approximately 4 h and thereafter decline with measured half-lives averaging up to 14 h. However, accumulation with daily dosing achieves steady state in 6-7 days, which suggests a true elimination half-life on the order of 24 h. Administration of the same daily dose in a BD schedule results in 2-fold greater systemic exposure than a OD schedule. Despite this inconsistency, systemic exposure generally increases with increasing dose. Absorption is increased by ingestion with food. Elimination of Lapatinib is predominantly through metabolism by CYP3A4/5 with negligible renal excretion. Significant changes in systemic exposure to Lapatinib result from co-administration of drugs that are potent inhibitors or inducers of CYP3A.

10.2.23Human Toxicity

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

Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. *Frequency is provided based on 975 patients*. Below is the CAEPR for lapatinib (GW572016).

Version 2.2, March 5, 2008[1]

Adverse Events with Possible Relationship to Lapatinib (GW572016) (CTCAE v3.0 Term) [n=975 patients]			**'Agent Specific Adverse Event List' (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC ARRHYTHMIA			
		Prolonged QTc interval	***Prolonged QTc interval***
CARDIAC GENERAL			
		Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction***
CONSTITUTIONAL SYMPTOMS			
Fatigue (asthenia, lethargy, malaise)			***Fatigue (asthenia, lethargy, malaise)***
	Weight loss		
DERMATOLOGY/SKIN			
	Flushing		***Flushing***
	Pruritus/itching		***Pruritus/itching***
Rash/desquamation			***Rash/desquamation***
	Rash: acne/acneiform		***Rash: acne/acneiform***
GASTROINTESTINAL			
	Anorexia		***Anorexia***
	Dehydration		***Dehydration***
Diarrhea			***Diarrhea***
	Distension/bloating, abdominal		***Distension/bloating, abdominal***
	Flatulence		***Flatulence***
	Heartburn/dyspepsia		***Heartburn/dyspepsia***
	Mucositis/stomatitis (clinical exam) - Select		***Mucositis/stomatitis (clinical exam) - Select***
	Mucositis/stomatitis (functional/symptomatic) - Select		***Mucositis/stomatitis (functional/symptomatic) - Select***
Nausea			***Nausea***
	Taste alteration (dysgeusia)		***Taste alteration (dysgeusia)***

	Vomiting		***Vomiting***
HEPATOBILIARY/PANCREAS			
		Liver dysfunction/failure (clinical)	***Liver dysfunction/failure (clinical)***
METABOLIC/LABORATORY			
	ALT, SGPT (serum glutamic pyruvic transaminase)		***ALT, SGPT (serum glutamic pyruvic transaminase)***
	AST, SGOT (serum glutamic oxaloacetic transaminase)		***AST, SGOT (serum glutamic oxaloacetic transaminase)***
	Bilirubin (hyperbilirubinemia)		***Bilirubin (hyperbilirubinemia)***
PAIN			
	Pain - Abdomen NOS		***Pain - abdomen NOS***
	Pain - Head/headache		***Pain - head/headache***
PULMONARY/UPPER RESPIRATORY			
		Pneumonitis/pulmonary infiltrates	
SYNDROMES			
	Flu-like syndrome		***Flu-like syndrome***

[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.

Also reported on lapatinib (GW572016) trials but with the relationship to lapatinib (GW572016) still undetermined:

ALLERGY/IMMUNOLOGY - allergic reaction

BLOOD/BONE MARROW - hemoglobin; leukopenia; lymphopenia; platelets; neutrophils/granulocytes

CARDIAC ARRHYTHMIA - atrial fibrillation

CARDIAC GENERAL - cardiac failure; cardiomyopathy; hypotension

CONSTITUTIONAL SYMPTOMS - fever; insomnia

DEATH - sudden death

DERMATOLOGY/SKIN - dry skin; hand-foot skin reaction; nail changes; urticaria

GASTROINTESTINAL - constipation; gastro-esophageal reflux disease (gastritis); intestinal obstruction

HEMORRHAGE/BLEEDING - CNS hemorrhage; GI hemorrhage; nose hemorrhage (epistaxis);

LYMPHATICS - limb edema

METABOLIC/LABORATORY - alkaline phosphatase; hyperglycemia; hypoglycemia; hypokalemia; hyponatremia; hypophosphatemia

NEUROLOGY - coma; dizziness

OCULAR/VISUAL - blurred vision

PAIN - back pain; joint pain; pain NOS; muscle pain

PULMONARY/UPPER RESPIRATORY - cough; dyspnea

VASCULAR – hypovolemia; pulmonary embolism

Note: The following additional adverse events have been reported from all lapatinib studies (Periodic Safety Report to Investigators) as suspected and unexpected serious adverse reactions; acute respiratory failure, lung abscess, hemoptysis, laryngeal edema,dysphagia, odynophagia, hypertension,cardiac neoplasm, pericarditis, myocardial infarction, shock, GI infection, colitis, hematochezia, hematemesis, dehydration, renal failure, renal impairment, dysuria, facial swelling, hepatic failure, leukocytoclastic vasculitis, syncope, shingles, cellulitis, hypothyroidism, thyroiditis, alkaline phosphatase level increase, gamma-glutamyltransferase level increase, hypercreatinemia, myocarditis, abnormal behavior, confusional state, coronary artery disease, atrial fibrillation, urinary tract infection, polyneuropathy, cerebrovascular ischemia, oral cavity hemorrhage, aplasia, anal fissure, deep vein thrombosis-limb, disseminated intravascular coagulation, hand-foot syndrome, viral infection, cardiac infection, respiratory tract infection, peripheral neuropathy, and chronic hepatitis.

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.

Note: There is a chemical that is present in lapatinib in small quantities. This chemical by itself may cause changes to genes (DNA--the genetic material of cells) that may lead to an increased chance of developing new cancer or tumors.

11 REFERENCES

Allred, D. C., S. K. Mohsin, et al. (2001). "Histological and biological evolution of human premalignant breast disease." Endocr Relat Cancer **8**(1): 47-61.

Armstrong, C., Mollman, J., Corn, B.W., Alavi, J., Grossman, M. (1993). "Effects of radiation therapy on adult brain behavior: evidence for a rebound phenomenon in a Phase I trial." Neurology **43**(1961-1965).

Armstrong, T. S., T. R. Mendoza, et al. (2006). "Validation of the M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT)." J Neurooncol **In press**.

Bacus, S. S., A. V. Gudkov, et al. (2000). "Expression of erbB receptors and their ligands in breast cancer: implications to biological behavior and therapeutic response." Breast Dis **11**: 63-75.

Bence, A. K., E. B. Anderson, et al. (2005). "Phase I pharmacokinetic studies evaluating single and multiple doses of oral GW572016, a dual EGFR-ErbB2 inhibitor, in healthy subjects." Invest New Drugs **23**(1): 39-49.

Brandes, A. A., G. Cavallo, et al. (2005). "A multicenter retrospective study of chemotherapy for recurrent intracranial ependymal tumors in adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia." Cancer **104**(1): 143-8.

Burgess, A. W., H. S. Cho, et al. (2003). "An open-and-shut case? Recent insights into the activation of EGF/ErbB receptors." Mol Cell **12**(3): 541-52.

Burris, H. A., 3rd, H. I. Hurwitz, et al. (2005). "Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas." J Clin Oncol **23**(23): 5305-13.

Carmichael, J., U. Fink, et al. (1996). "Phase II study of gemcitabine in patients with advanced pancreatic cancer." Br J Cancer **73**(1): 101-5.

CBTRUS (2005). Statistical Report: Primary Brain Tumors in the United States, 1998-2002. Hinsdale, IL. USA, Central Brain Tumor Registry of the United States.

De Bustos, C., A. Smits, et al. (2005). "A PDGFRA promoter polymorphism, which disrupts the binding of ZNF148, is associated with primitive neuroectodermal tumours and ependymomas." J Med Genet **42**(1): 31-7.

Gilbert, M. R., H. S. Friedman, et al. (2002). "A phase II study of temozolomide in patients with newly diagnosed supratentorial malignant glioma before radiation therapy." Neuro-oncol **4**(4): 261-7.

Gilbertson, R. J., L. Bentley, et al. (2002). "ERBB receptor signaling promotes ependymoma cell proliferation and represents a potential novel therapeutic target for this disease." Clin Cancer Res **8**(10): 3054-64.

Graus-Porta, D., R. R. Beerli, et al. (1997). "ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling." Embo J **16**(7): 1647-55.

Groves, M. D., V. K. Puduvalli, et al. (2002). "Phase II trial of temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme." J Clin Oncol **20**(5): 1383-8.

Haas-Kogan, D. A., M. D. Prados, et al. (2005). "Epidermal growth factor receptor, protein kinase B/Akt, and glioma response to erlotinib." J Natl Cancer Inst **97**(12): 880-7.

Hendriks, B. S., L. K. Opresko, et al. (2003). "Quantitative analysis of HER2-mediated effects on HER2 and epidermal growth factor receptor endocytosis: distribution of homo- and heterodimers depends on relative HER2 levels." J Biol Chem **278**(26): 23343-51.

Jaeckle, K. A., K. R. Hess, et al. (2003). "Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study." J Clin Oncol **21**(12): 2305-11.

Kieran, M. W., R. J. Packer, et al. (2007). "Phase I and pharmacokinetic study of the oral farnesyltransferase inhibitor lonafarnib administered twice daily to pediatric patients with advanced central nervous system tumors using a modified continuous reassessment method: a Pediatric Brain Tumor Consortium Study." J Clin Oncol **25**(21): 3137-43.

Kleihues, P. and W. K. Cavenee, Eds. (2000). Pathology and Genetics of Tumours of the Nervous System. World Health Organization Classification of Tumours. Lyon, IARC Press.

Korshunov, A., K. Neben, et al. (2003). "Gene expression patterns in ependymomas correlate with tumor location, grade, and patient age." Am J Pathol **163**(5): 1721-7.

Lamszus, K., L. Lachenmayer, et al. (2001). "Molecular genetic alterations on chromosomes 11 and 22 in ependymomas." Int J Cancer **91**(6): 803-8.

Maksoud, Y. A., Y. S. Hahn, et al. (2002). "Intracranial ependymoma." Neurosurg Focus **13**(3): e4.

Mellinghoff, I. K., M. Y. Wang, et al. (2005). "Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors." N Engl J Med **353**(19): 2012-24.

Merchant, T. E. and M. Fouladi (2005). "Ependymoma: new therapeutic approaches including radiation and chemotherapy." J Neurooncol **75**(3): 287-99.

Michalowski, M. B., F. de Fraipont, et al. (2006). "Methylation of RASSF1A and TRAIL pathway-related genes is frequent in childhood intracranial ependymomas and benign choroid plexus papilloma." Cancer Genet Cytogenet **166**(1): 74-81.

Moynihan, T. J. (2003). "Ependymal tumors." Curr Treat Options Oncol **4**(6): 517-23.

Rehman, S., C. Brock, et al. (2006). "A case report of a recurrent intracranial ependymoma treated with temozolomide in remission 10 years after completing chemotherapy." Am J Clin Oncol **29**(1): 106-7.

Rusnak, D. W., K. Lackey, et al. (2001). "The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo." Mol Cancer Ther **1**(2): 85-94.

Shewchuk, L., A. Hassell, et al. (2000). "Binding mode of the 4-anilinoquinazoline class of protein kinase inhibitor: X-ray crystallographic studies of 4-anilinoquinazolines bound to cyclin-dependent kinase 2 and p38 kinase." J Med Chem **43**(1): 133-8.

Stupp, R., W. P. Mason, et al. (2005). "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma." N Engl J Med **352**(10): 987-96.

Suarez-Merino, B., M. Hubank, et al. (2005). "Microarray analysis of pediatric ependymoma identifies a cluster of 112 candidate genes including four transcripts at 22q12.1-q13.3." Neuro Oncol **7**(1): 20-31.

Tolcher, A. W., S. L. Gerson, et al. (2003). "Marked inactivation of O6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules." Br J Cancer **88**(7): 1004-11.

Wick, A., J. Felsberg, et al. (2007). "Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma." J Clin Oncol **25**(22): 3357-61.

Xia, W., R. J. Mullin, et al. (2002). "Anti-tumor activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways." Oncogene **21**(41): 6255-63.

Yarden, Y. and M. X. Sliwkowski (2001). "Untangling the ErbB signalling network." Nat Rev Mol Cell Biol **2**(2): 127-37.

Yung, W. K., R. E. Albright, et al. (2000). "A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse." Br J Cancer **83**(5): 588-93.

Zhou, H., Y. S. Kim, et al. (2004). "Effects of the EGFR/HER2 kinase inhibitor GW572016 on EGFR- and HER2-overexpressing breast cancer cell line proliferation, radiosensitization, and resistance." Int J Radiat Oncol Biol Phys **58**(2): 344-52.

12 APPENDICES

12.1 KARNOFSKY PERFORMANCE SCALE, NEUROLOGICAL FUNCTION, AND MENTAL STATUS

Patient's performance status will be graded according to the following scale:

Karnofsky Performance Status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death no imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Dead

Neurologic Function

☐	+2	Definitely Better
☐	+1	Possibly Better
☐	0	Unchanged
☐	-1	Possibly Worse
☐	-2	Definitely Worse
☐	B	Baseline

12.2 LAPATINIB PROHIBITED MEDICATION LIST

Drugs known to be metabolized by CYP450 isoenzyme 3A4
The following list of CYP3A4 inducers and inhibitors are prohibited from registration through discontinuation from study. Additionally, medications that modify gastric pH are included in the Miscellaneous section of the Table.

Drug Class	Agent	Wash-out
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine, rifampin)	14 days
Anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital) , oxcarbazepine	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin, telithromycin, ciprofloxacin norfloxacin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	Aprepitant, cimetidine	
Other	grapefruit, grapefruit juice, Bitter Orange	
	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennies H2 Blockers: ranitidine, nizatidine, famotidine Protocon Pump Inhibitors: omeprazole, esomeprazole, rabeprazole, pantoprazole, lansoprazole	Excluded 1 hour before and after dosing
GI Agents	cimetidine	48 hours
At screening, if a patient is receiving any of the above medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to registration on study and throughout the study period in order for the patient to be eligible to participate in the study.		

12.3 TREATMENT DIARY FOR ORAL LAPATINIB & TEMOZOLOMIDE

PATIENT NAME: _____ I.D. # _____ CYCLE# _____ PAGE 1 OF 2

This calendar is for you to indicate that you took the drug(s) according to the instructions. Please put a check mark or your initials after each dose.

Please sign this calendar at the end of the cycle and bring the calendar and all study drug bottle(s) back to your next clinic visit.

DOSES: Lapatinib _____mg by mouth every AM

Temozolomide _____ mg by mouth once a day for 7 days every 2 weeks.

Day 1 _____ LAP a.m. _____ TMZ _____	Day 2 _____ LAP a.m. _____ TMZ _____	Day 3 _____ LAP a.m. _____ TMZ _____	Day 4 _____ LAP a.m. _____ TMZ _____	Day 5 _____ LAP a.m. _____ TMZ _____	Day 6 _____ LAP a.m. _____ TMZ _____	Day 7 _____ LAP a.m. _____ TMZ _____
Day 8 _____ LAP a.m. _____	Day 9 _____ LAP a.m. _____	Day 10 _____ LAP a.m. _____	Day 11 _____ LAP a.m. _____	Day 12 _____ LAP a.m. _____	Day 13 _____ LAP a.m. _____	Day 14 _____ LAP a.m. _____
Day 15 _____ LAP a.m. _____ TMZ _____	Day 16 _____ LAP a.m. _____ TMZ _____	Day 17 _____ LAP a.m. _____ TMZ _____	Day 18 _____ LAP a.m. _____ TMZ _____	Day 19 _____ LAP a.m. _____ TMZ _____	Day 20 _____ LAP a.m. _____ TMZ _____	Day 21 _____ LAP a.m. _____ TMZ _____
Day 22 _____ LAP a.m. _____	Day 23 _____ LAP a.m. _____	Day 24 _____ LAP a.m. _____	Day 25 _____ LAP a.m. _____	Day 26 _____ LAP a.m. _____	Day 27 _____ LAP a.m. _____	Day 28 _____ LAP a.m. _____

My signature signifies that the study drug(s) have been taken as indicated:

Signature of Patient: _____ Date: _____

12.4 PILL COUNT DOCUMENTATION:

TO BE COMPLETED BY CLINICAL RESEARCH STAFF

PATIENT NAME: ___________________________ I.D. # _________ CYCLE# ________

DOSE OF LAPATINIB PRESCRIBED: __________ MG, PO, Every AM for 28 days EVERY cycle (1 cycle = 28 days).

LAPATINIB is supplied in Tablet strengths of 250mg.

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

DATE DISPENSED: _____________ (mm/dd/yy)

QUANTITY OF BOTTLES DISPENSED: ________- QUANTITY OF 250MG TABLETS DISPENSED: ___________

NUMBER OF 250MG TABLETS PER DAY REQUIRED TO ACHIEVE PRESCRIBED DOSE:

____

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

**********DO NOT RETURN UNUSED TABLETS TO THE PATIENT*************

RETURN PILL/BOTTLE COUNT DATE: ___________ Has the patient taken the dose scheduled for this date? YES NO

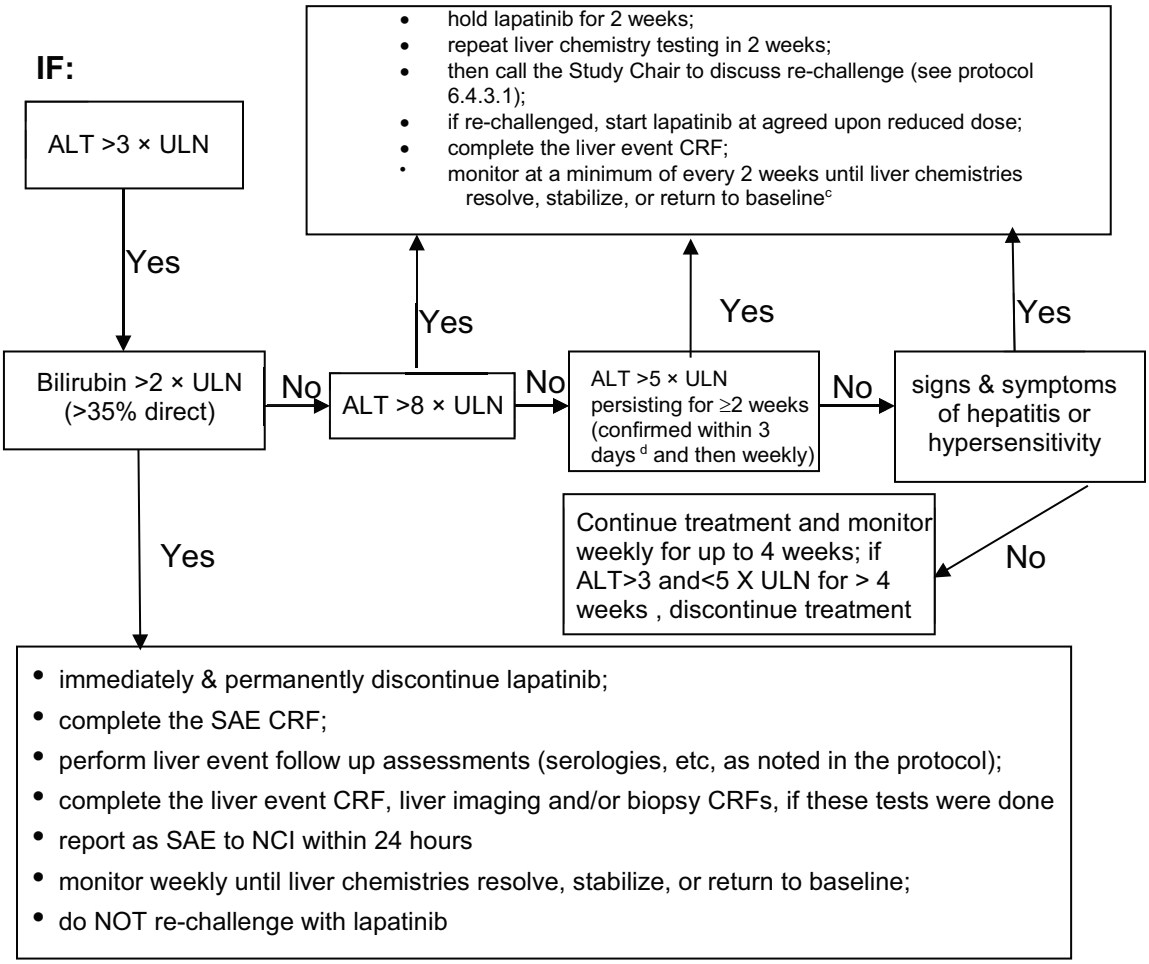
(mm/dd/yy)

QUANTITY OF BOTTLES RETURNED: _____________QUANTITY OF TABLETS RETURNED: ______________

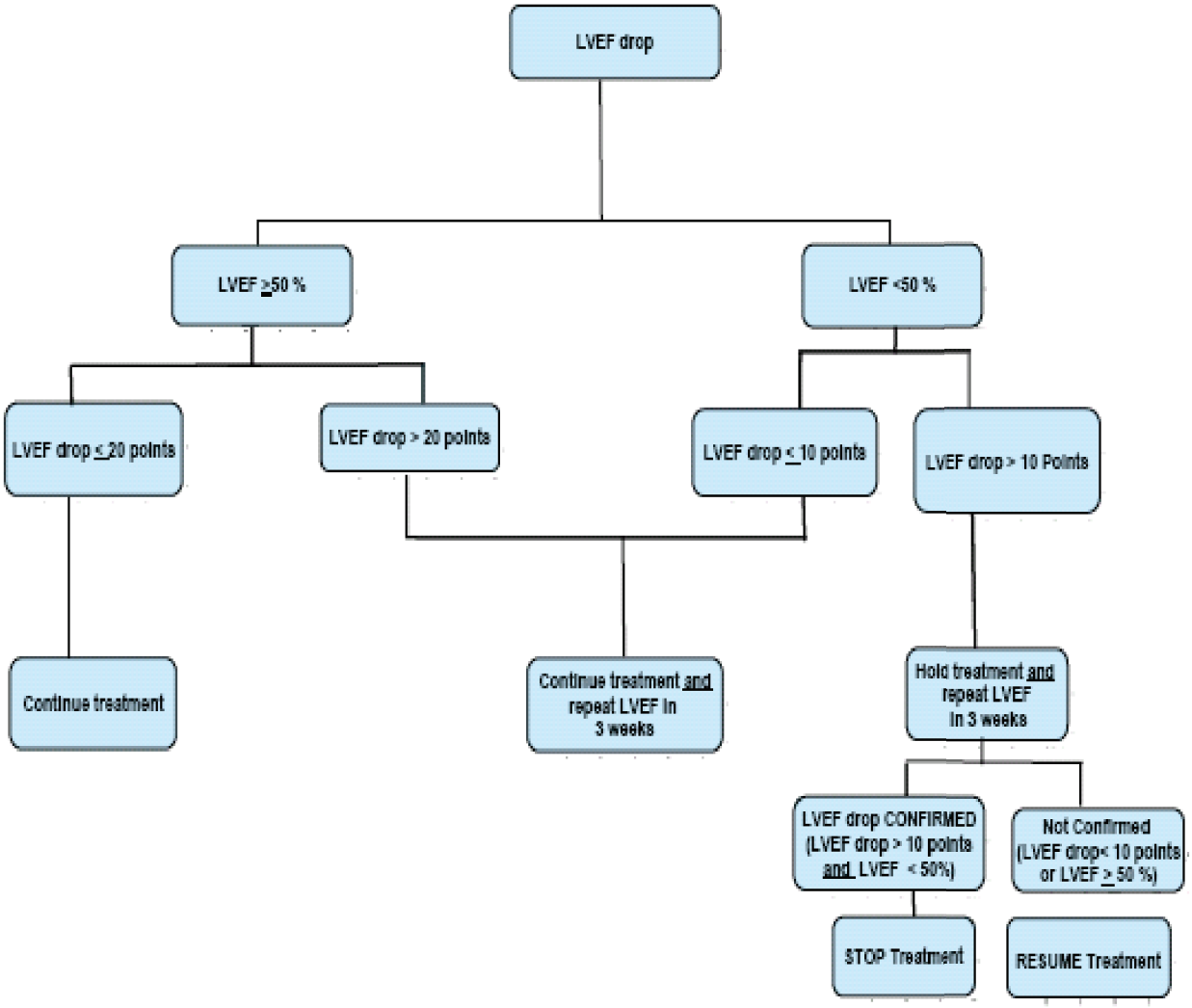
____ ____________ _________________________________

SIGNATURE OF PHARMACY OR RESEARCH STAFF DATE PHONE #

12.5 LIVER CHEMISTRY STOPPING AND FOLLOW UP CRITERIA



12.6 LEFT VENTRICULAR EJECTION FRACTION (LVEF) ASSESSMENT ALGORITHM



12.7 MD ANDERSON SYMPTOM INVENTORY FOR BRAIN TUMORS (MDASI-BT)

MDASI BT 1726 **Date:** (month) / (day) (Year)

Protocol Number:

Participant's Initials:

PLEASE USE A BLACK INK PEN

Patient #:

Protocol Acc # :

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

Part I. How severe are your symptoms?

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

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

1726 Date: (Month) / (Day) (Year)

MDASI BT

Initials:

Patient #:

PLEASE USE A BLACK INK PEN

Protocol Acc # :

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

Part II. How have your symptoms interfered with your life?

Symptoms frequently interefere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

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

12.8 MD ANDERSON SYMPTOM INVENTORY FOR SPINE TUMORS (MDASI-SP).

33053 MDASI SP Date: ☐☐ / ☐☐ ☐☐☐☐ (month) (day) (Year)

Protocol Number

Participant's Initials: ☐☐☐

PLEASE USE A BLACK INK PEN

Patient #: ☐☐☐☐☐☐

Protocol Acc # : ☐☐☐☐

M.D. Anderson Symptom Inventory - Spine Tumor (MDASI-SP)

Part I. How severe are your symptoms?

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

CORE Items	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You can Imagine 10
1. Your pain at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your fatigue (tiredness) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your nausea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your disturbed sleep at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being distressed (upset) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your shortness of breath at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with remembering things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with lack of apetite at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling drowsy (sleepy) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a dry mouth at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling sad at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your vomiting at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your numbness or tingling at its WORST?	○	○	○	○	○	○	○	○	○	○	○

33053 Date: (month) / (Day) (Year) MDASI SP

Participant's Initials

PLEASE USE A BLACK INK PEN **Patient #:** **Protocol Acc # :**

SPINE Tumor Specific Items	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You can Imagine 10
14. Your radiating spine pain at its WORST?	O	O	O	O	O	O	O	O	O	O	O
15. Your weakness in the arms and/or legs at its WORST?	O	O	O	O	O	O	O	O	O	O	O
16. Your loss of control of bowel and/or bladder at its WORST and/or legs at its WORST?	O	O	O	O	O	O	O	O	O	O	O
17. Your change in bowel pattern(diarrhea/constipation) at its WORST?	O	O	O	O	O	O	O	O	O	O	O
18. Your sexual function at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Part II. How have your symptoms interfered with your life?

Symptoms frequently interefere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
19. General activity ?	O	O	O	O	O	O	O	O	O	O	O
20. Mood ?	O	O	O	O	O	O	O	O	O	O	O
21. Work (including work around the house) ?	O	O	O	O	O	O	O	O	O	O	O
22. Relations with other people?	O	O	O	O	O	O	O	O	O	O	O
23. Walking?	O	O	O	O	O	O	O	O	O	O	O
24. Enjoyment of life ?	O	O	O	O	O	O	O	O	O	O	O

12.9 CCR PROBLEM REPORT FORM

<table>
<tr><td>NCI Protocol #:</td><td>Protocol Title:</td></tr>
<tr><td></td><td>Report version: (select one)
____Initial Report
____Revised Report
____Follow-up</td></tr>
<tr><td>Site Principal Investigator:</td><td></td></tr>
<tr><td>Date of problem:</td><td>Location of problem: (e.g., patient's home, doctor's office)</td></tr>
<tr><td colspan="2">Who identified the problem? (provide role (not name of person): nurse, investigator, monitor, etc…)</td></tr>
<tr><td>Brief Description of Subject (if applicable)
(Do NOT include personal identifiers)</td><td>Sex: ___ Male ___ Female Age:
___ Not applicable (more than subject is involved)</td></tr>
<tr><td colspan="2">Diagnosis under study:</td></tr>
<tr><td colspan="2">Name the problem: (select all that apply)
[ ] Adverse drug reaction
[ ] Abnormal lab value
[ ] Death
[ ] Cardiac Arrest/ code
[ ] Anaphylaxis
[ ] Sepsis/Infection
[ ] Blood product reaction
[ ] Unanticipated surgery/procedure
[ ] Change in status (e.g. increased level of care required)
[ ] Allergy (non-medication)
[ ] Fall
[ ] Injury/Accident (not fall)
[ ] Specimen collection issue
[ ] Informed consent issue
[ ] Ineligible for enrollment
[ ] Breach of PII
[ ] Tests/procedures not performed on schedule
[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (Include any relevant treatment, outcomes or pertinent history):</td></tr>
<tr><td colspan="2">*Is this problem unexpected? (see the definition of unexpected in the protocol)) __YES __NO Please explain:</td></tr>
</table>

*Is this problem related or possibly related to participation in the research? __YES __NO Please explain:
*Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized? __YES __NO Please explain:
Is this problem? (*select all that apply*) [ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO If "Yes", how many? ____ Please describe:
Describe what steps you have already taken as a result of this problem:
In addition to the NCI IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	DATE: