TITLE: **A Phase II Study to Determine the Efficacy of Tarceva (Erlotinib Hydrochloride) with Concurrent Whole Brain Radiation Therapy in Patients with Brain Metastases from Non-Small Cell Lung Cancer**

PROTOCOL NO. **2008-0170 (OSI-774UA2005)**

SPONSOR: **M. D. Anderson Cancer Center (MDACC)**

Pharmaceutical: **OSI Pharmaceuticals**

STUDY DRUG: **Tarceva (Erlotinib Hydrochloride: OSI-774)**

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1.0 Introduction

Lung cancer is the leading cause of worldwide cancer mortality, and is responsible for more deaths annually in the United States than the combination of breast, colorectal, and prostate cancer, with an estimated 1.04 million new cases each year worldwide (1-4). Non–small cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers, and of these approximately one third will develop brain metastasis at some time during the course of their disease. Additionally, 50% of all brain metastases are from lung primary tumors (5-7). Unfortunately, for the vast majority of these patients this diagnosis is associated with significant impairment and morbidity and drastically shortened survival. Present treatments for brain metastases include Surgery, Whole Brain Radiation Therapy (WBRT) and Stereotactic Radiosurgery (SRS). These modalities are often quite effective in alleviating symptoms; however, median survival remains poor, at around 2-7 months, (8) clearly new treatments are greatly needed.

1.1 Rationale:

The process of cell division, growth, differentiation and death is a highly regulated process. Several classes of trans-membrane receptors play a pivotal role in this process. Of these, epidermal growth factor receptor (EGFR) a member of Receptor Tyrosine Kinase (RTK) family is best known. This family is comprised of four receptors Erb B1/HER 1, Erb B2 / HER 2, Erb B3/ HER 3, and Erb B4 / HER 4. Activation of these receptors typically occurs via specific ligand binding, resulting in the hetero- or homodimerization between receptor family members, with subsequent autophosphorylation of the tyrosine kinase domain. This activation triggers a cascade of intracellular signaling pathways involved in both cellular proliferation (ras/raf/MAP kinase pathway) and survival (PI3kinase/AKT pathway).

Aberrant signaling through the epidermal growth factor receptor (EGFR) is associated with neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis, angiogenesis and metastatic spread (9). The critical role that EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclinical studies and the early clinical trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. Furthermore, continuous stimulation of the EGFR-mediates signal transduction pathway may not only confer a growth advantage to malignant cells, but also a survival advantage following a genotoxic insult such as ionizing radiation (anti-apoptotic effects) (10).

Efficacy of this approach has been demonstrated in breast cancer with the blocking of the HER-2 receptor with the monoclonal antibody Herceptin. An alternate strategy is to inhibit EGFR TK activity using small molecules, like OSI-774 (Erlotinib, Tarceva™; OSI Pharmaceuticals) or ZD 1839 (gefitinib, Iressa™; Astra Zeneca) approved for use in lung cancer. Tarceva acts by reversibly inhibiting EGFR-TK thus inhibiting autophosphorylation of EGFR. Initial trials of daily oral Tarceva 150 mg QD (Study 248-1007) enrolled 56 patients with diagnosis NSCLC showed a 14.3% objective response rate and a 28.6% rate of disease stabilization. Tarceva was well tolerated and demonstrated predictable pharmacokinetics. Additionally, Tarceva was assessed in a Phase III, randomized, double-blind, placebo-controlled trial in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. In a 2:1 randomization (Tarceva: Placebo), patients received Tarceva 150 mg or placebo orally once daily until disease progression or unacceptable toxicity. The primary study endpoint was survival with additional endpoints of response rate and progression free survival. The results of the study indicated a statistically significant improvement in survival for Tarceva treated patients (6.7 mo vs 4.7 mo). Both secondary endpoints (PFS and Response) also favored the Tarceva arm with p value <0.001 (11).

Given that Tyrosine Kinase Inhibitors (TKIs) have been shown to have efficacy in patients with Non-Small Cell Lung Cancer (NSCLC), one would postulate that metastases from NSCLC primaries would also likely respond. NSCLC has a propensity to metastasize to the Central Nervous System (CNS). One of the greatest barriers in treating CNS malignancies lies in the limited drug penetration through the blood brain barrier (making therapeutics such as mAB's essentially useless in the brain). However, Heimberger et al, at Duke has shown that small molecule TKIs (ZD1839) not only cross the BBB but produce a 105% increase in survival in animal models with brain tumors compared to untreated controls (12). Furthermore, work published in our lab has demonstrated that the use of TKIs in vitro had a significant radiosensitizing effect and increased cell death when combined with external beam radiation (13). Furthermore, this synergistic effect of combining tyrosine kinase inhibitors and external beam radiation have been suggested by Bonner et al, work in head and neck cancer, that was recently presented in the Journal of Clinical Oncology (14). Lastly, the safety of combining Tarceva and external beam radiation in treating Central Nervous System (CNS) tumors has been recently demonstrated in a phase I study (15). In this dose escalation study with 20 patients with glioblastoma multiforme, Tarceva was dose escalated up to 200 mg per day, concurrently with external beam radiation of 60 Gy. Of the twenty patients, only one experienced a dose limiting toxicity of stomatitis. Given that we will be using a lower dose of both Tarceva and radiation (150 mg and 30 Gy respectively), we feel that this is a safe regimen.

Based on these observations, we hypothesized that the synergistic properties of TKIs along with external beam radiation may prove to be a well tolerated and efficacious means of extending overall survival and decreasing morbidity in patients with brain metastasis from NSCLC.

2.0 Study Objectives

2.1 Primary Endpoints:

To determine if Tarceva, given orally on a daily basis along with concurrent whole brain radiation therapy improves median survival of patients with brain metastases, compared with historical controls.

2.2 Secondary Endpoints:

2.2.1 To see if Tarceva along with concurrent WBRT, improves quality of life as assessed with the Spitzer Quality of Life Index (Appendix E) and the Folstein Mini-Mental Status Exam (Appendix F). Optional test will include Digit Span, Digit Symbol, Hopkins Verbal Learning Test, Controlled Oral Word Association, Trail Making Test Part A, Trail Making Test Part B, Grooved Pegboard, Barthel ADL Index, M.D. Anderson Symptom Inventory, and Functional Assessment of Cancer Therapy with Brain Module. As of July 18, 2012- Optional tests will no longer be completed.

2.2.2 To see if Tarceva along with concurrent WBRT, influences cause of death compared to matched controls, based on key attributes such as stage, age KPS, number of brain metastasis, etc.

2.2.3 To see if Tarceva along with concurrent WBRT, increases time to progression of disease.

2.2.4 To sequence the EGFR receptor of patients treated with Tarceva, in order to identify specific gene mutations that may correlate with favorable responses to Tarceva.

2.2.5 To study downstream proteins involved in the EGFR cascade such as p-EGFR, Raf, PKC, JNK, and p-AKT. This information will be combined with other protein markers such as E cadherin that appear to increase the probability of response, in the hopes of developing a genetic signature of patients most likely to benefit from this regimen.

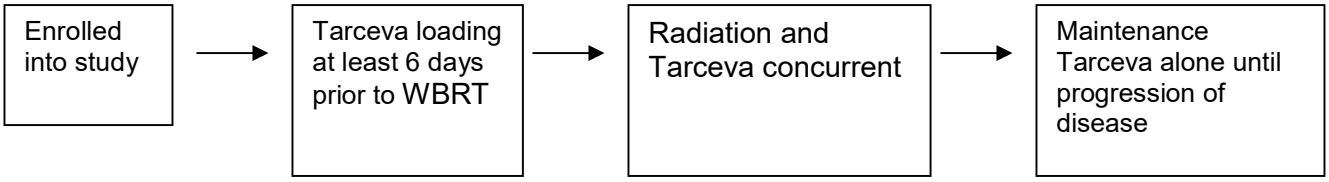
2.2.6 To confirm the safety profile of Tarceva along with concurrent external beam radiation therapy, in the context of treating central nervous system malignancies.

2.2.7 To provide evidence to support a much larger multi-institutional study.

3.0 Study Design

Twenty patients will be collected from this M.D. Anderson based study and the data will be combined with an identical 20 patient study that Dr. James Welsh started while at the Arizona Cancer Center. The Arizona study has enrolled 15 of the planned 20 patients (as of August 2008), and by combining these two studies we will have a total of 40 patients for final analysis.

Study Schema



Patients must have radiographic evidence of brain metastases, proven with CT or MRI so that we can stratify patients by the number of brain metastases. Additionally, they must have no prior history of cranial radiation (other than stereotactic radiosurgery). Once enrolled, patients will receive Tarceva (150mg PO QD) for at least 6 days prior to starting and during whole brain radiotherapy (WBRT). External beam radiation will consist of opposed laterals to a total dose of 3500cGy in 14 daily fractions.

Upon completion of external whole brain radiation, patients will continue taking Tarceva (150mg PO QD) until documentation of disease progression (unless treating physician feels that stopping Tarceva would adversely affect the patient) or if patients are unable to tolerate study drug due to toxicities. Patients will be allowed to stop taking Tarceva at any time during this trial. Following completion of WBRT patients will have a repeat MRI or CT at 1 month after completion of WBRT, and then at 3 month intervals, or sooner if indicated by symptom progression. Additionally, during active treatment period of this trial, patients will not be allowed to have surgical debulking of CNS tumors, or stereotactic radiosurgery of CNS lesions, as this need would correlate with progression of disease. Patients will be allowed to receive palliative radiation if needed to address symptoms. Patients will be allowed to dose reduce down to 50mg per day, and may also take a treatment break of up to seven days.

Survival will be compared to a database of patients with similar histologies and stratified according to their Recursive Partitioning Analysis (RPA) class and the number of brain metastases, at time of diagnosis (16). The RPA is a predictive tool used to estimate survival based on age, performance status, and presence of extracranial metastasis.

The vast majority of patient will either be and RPA class I or II, which predicts for a survival of 7.1 and 4.2 months respectively. Patients that elect for tumor protein expression analysis will go on to have their tumors tested for EGFR expression along with receptor sequencing, if possible. This will serve to identify if specific gene mutations may correlate with favorable responses to Tarceva. Additionally, we will also study proteins thought to predict anti-EGFR response such as Vimentin, E-Cadherin, Fibronectin, PTEN, PKC, c-Met and p-AKT. This information will be use to determine if a genetic signature of patients most likely to benefit from this regimen can be identified.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

4.1.1 Histological confirmation of non-small cell lung cancer

4.1.2 Patients who have been treated in the past with Stereotatic radiosurgery, Stereotactic Radiotherapy, GliaSite or surgical resection will be allowed to enroll in this study

4.1.3 A diagnostic contrast-enhanced MRI or CT scan must be performed, demonstrating brain metastases

4.1.4 Age 18-70

4.1.5 Patients must have KPS ≥ 70

4.1.6 Patients cannot be treated on any other treatment related clinical protocols within 30 days prior to study entry or during participation in the study

4.1.7 No uncontrolled or symptomatic major medical illnesses or psychiatric impairments, such as Alzheimer's or schizophrenia

4.1.8 Screening Clinical Laboratory Values: ANC >1500/ul, Platelets >80,000/ul, baseline AST and/or ALT within normal limits (within 30 days of starting protocol treatment).

4.1.9 All women of childbearing potential (A woman of child-bearing potential is a sexually mature woman who has not undergone a hysterectomy or who has not been naturally postmenopausal for at least 24 consecutive months [i.e., who has had menses at any time in the preceding 24 consecutive months]) and male participants must practice effective contraception (abstinence, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study. All women of child-bearing potential must have a negative serum pregnancy test and practice birth control while on study.

4.1.10 Patients must provide verbal and written informed consent to participate in the study

4.2 Exclusion Criteria

4.2.1 Prior cranial radiation therapy, other than stereotatic radiosurgery, Stereotactic Radiotherapy or GliaSite.

4.2.2 Patients with known Acquired Immune Deficiency *(AIDS),* as regimens with tyrosine kinase inhibitors may pose a safety risk related to excess toxicity or interference with anti-viral effectiveness

4.2.3 Women who are pregnant or lactating, due to possible adverse effects on the developing fetus or infant due to study drug

4.2.4 Patients with active connective tissue disorders, such as lupus or scleroderma

5.0 Study Medications

5.1 Description

Tarceva (Eroltinib Hydrochloride):
Tarceva is a quinazolinamine with the chemical name N-(3-ethynylphenyl)6,7 bis(2methoxyethoxy)-4-quniazolinamine and contains Erlotinib 2 Clinical Formulations. In addition to the active ingredient, Tarceva tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium sulfate. The molecular weight of Tarceva (Erlotinib) is 429.90. It is slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

5.2 Pharmacology

The mechanism of clinical antitumor activity of Tarceva is not fully characterized. Tarceva inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR).

Bioavailability of Tarceva following a 150mg oral dose is about 60% and peak plasma levels occur 4 hours after dosing. Food increases bioavailability substantially to almost 100%. Tarceva's half life is about 36 hours and it is cleared predominantly by CYP3A4 metabolism. Time to reach steady state plasma concentration is 7-8 days and no significant relationship has been observed of clearance to patient's age, body weight or gender. Smokers have a higher rate of Tarceva clearance than non-smokers. Tarceva is predominantly cleared by the liver. No data are currently available regarding the influence of hepatic dysfunction or hepatic metastases on the pharmacokinetics of Tarceva. Since Tarceva is predominantly metabolized by CYP3A4, inhibitors or inducers of CYP3A4 would be expected to increase and decrease exposure, respectively. A potential for drug-drug interaction exists when Tarceva is co-

administered with drugs that are highly protein bound or that are CYP3A4 and CYP1A2 inhibitors/inducers.

For patients who are being concomitantly treated with a potent CYP3A4 inhibitor, a dose reduction should be considered in the presence of severe adverse events. For patients who are being concomitantly treated with a potent CYP3A4 inducer, alternative treatments that lack potent CYP3A4-inducing properties should be considered.

Patients taking an enzyme-inducing anti-convulsant medication (phenytoin, carbamazepine, phenobarbital, Mysoline, Trileptal). It should be discontinued and converted to a nonenzyme-inducing anti-convulsant (Keppra, Depakote, Topamax, Lamictal or Neurontin) prior to the first dose of Tarceva.

In addition, altered coagulation parameters and bleeding have been reported in patients receiving Tarceva alone and in combination with other chemotherapeutic agents and concomitant warfarin-derivative anticoagulants. The mechanism for these alterations is still unknown. When warfarin is coadministered with Tarceva (anytime after Day 5), international normalized ratio (INR) and prothrombin time should be closely monitored (weekly until stabilized) and the anticoagulant dose should be adjusted as clinically indicated.

5.3 Adverse Events/Precautions

The most common adverse reactions in patients receiving Tarceva monotherapy and in combination with chemotherapy are rash and diarrhea. Grade 3-4 rash and diarrhea occurred in 9% and 6%, respectively in Tarceva treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of Tarceva treated patients. The median time to the onset of rash was 8 days and the median time to onset of diarrhea was 12 days.

There have been infrequent reports of ILD (interstitial lung disease) in patients receiving Tarceva for the treatment of NSCLC and other advanced solid tumors. In the randomized single agent study, the incidence of ILD (0.8%) was the same for both the placebo and Tarceva groups. The overall incidence of ILD from all studies was approximately 0.6%. If ILD is diagnosed, Tarceva should be discontinued and appropriate treatment instituted as necessary. There are no adequate and well controlled studies of Tarceva in pregnant women. Women of childbearing potential should be advised to avoid pregnancy while on Tarceva, and will need to practice brith control while on study, if premenopausal.

Asymptomatic increases in liver transaminases have been observed in patients on Tarceva; therefore, periodic liver function testing should be considered. Also, patients taking warfarin or other coumarin-derivative anti-coagulants should be monitored for

changes in prothrombin time or INR. NCI-CTC grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving Tarceva therapy. Corneal ulcerations may also occur.

5.4 Packaging, Supply, and Labeling
Tarceva (Erlotinib) will be supplied by OSI at no cost for each study patient. The pharmaceutical preparations of Tarceva are formulations containing the hydrochloride salt (OSI 774 01). Tarceva is supplied as tablets containing erlotinib hydrochloride equivalent to 150 mg, 100 mg, and 25 mg of erlotinib. All tablets are round, white, film-coated, bi-convex tablets without markings. Each bottle will be labeled with the drug name, pill dose, number of pills, manufacture date, Lot # and expiration date.

5.5 Storage
Tarceva tablets should be stored between 15°C and 30°C (59°F and 86°F).

5.6 Administration
Patients will receive only a 30-day supply of drug at a time, from the Investigational Pharmacy. The patient will be seen by the nurse once approximately every 30 days (+/- 7 days) to review number of pills taken during the previous 30 days (+/- 7 days), and to receive another 30 days of medication. If patients are unable to return for their follow up visits, we will review their mediations and current drug logs over the phone and their Tarceva refills will be mailed to them via the investigational pharmacy.

Patients will begin taking Tarceva at least 6 days before their first dose of radiation, daily during radiation therapy, and then daily until progression is documented (unless treating physician feels that stopping Tarceva would adversely affect the patient), adverse events warrant discontinuation or the patient decides to stop taking the medication.

Tarceva tablets should be taken once daily. Each Tarceva dose is to be taken with up to 200 mL (~ 1 cup or 8 oz) of water, and should be taken 1 hour before or 2 hours after meals or medications, including grapefruit juice, vitamins, and iron supplements.

For patients residing outside the U.S: Patients will receive a 90 day supply of Tarceva at a time, from the Investigational Pharmacy; The study PI will have physician-to-physician communication regarding protocol enrollment; a letter (Appendix G) will be sent to the home physician outlining the subject's participation and requesting the home physician agreement to supervise the subjects care. The home physician will be requested to provide any patient medication diaries, progress notes, hospitalization records, toxicities, tests, and procedures to the study PI or his research staff at MD Anderson within 48 hours. The home physician will be asked that any questions related to the study drug dosing, schedule, or side effects be directed to study PI. All life

threatening clinical events must be reported by the home physician to the study PI within 24 hours of documented occurrence. The home physician will be provided with study contact numbers for business and non-business hours.

Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

Patients will return to MDACC every 3 months for evaluation.

5.7 Accountability

In accordance with current Good Clinical Practices (GCPs), the investigational site will account for all supplies of Tarceva. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the investigational site. The drug will be delivered to and distributed by the investigational pharmacy of MD Anderson for clinical investigations.

All unused supplies of Tarceva (from the study and unused drug from patients) will be destroyed after completion of the trial, as per pharmacy SOPs. Copies of the study drug accountability record will be provided to OSI Pharmaceuticals. Patients unused drug will be returned to the research nurse.

6.0 Study Methods

Study Calendar

Assessment	Screening	Baseline (1-3 days prior to day 1 of Tarceva)	Weekly During treatment	One Month Post RT (+/- 7 days)	Follow-up for patients on Tarceva (+/- 7 days)	Follow-up for patients off Tarceva (+/- 14 days)[m,n,o]

Histological confirmation of NSCLC	X					
CT/MRI of brain and report	X[b]			X	X[m]	X
CBC/Differential	X[b]					
Platelet	X[b]					
Complete Metabolic panel)	X[b]					
Repeat sodium level			X[e]			
CT or PET of Liver	X[c]					
Medical History	X	X[d]			X[d,f]	X[d]
Physical Examination	X[b]		X	X	X[m]	X
Concomitant Medications	X	X	X	X	X[a,f,]	
Serum Pregnancy test, if applicable	X[i]					

Assessment	Screening	Baseline (1-3 days prior to day 1 of Tarceva)	Weekly During treatment	One Month Post RT (+/- 7 days)	Follow-up for patients on Tarceva (+/- 7 days)	Follow-up for patients off Tarceva (+/- 14 days)[m,n,o]
Document steroid dose		X	X	X		
Spitzer Quality of Life Index		X[k]	X[l]			
Folstein Mini-Mental Status Exam		X[k]	X[l]			
Optional neurocognitive tests [p]		X[k]				
Consent for EGFR expression testing (Optional)	X					
Informed Consent	X					
Vital Signs		X		X	X[m]	X
Adverse Event Check [g]			X	X	X[f]	X
PT/INR if patient on Coumadin	X		X[h,j]	X[h]	X[h]	X

a = until 30 days after last dose of Tarceva
b = within 30 days of starting treatment
c = within 3 months of starting treatment
d = update only
e = Patient will have repeat sodium on RT day 7 and RT day 14 if baseline sodium $\leq$ 135 mg/dl
f= Patients will be seen by the research nurse monthly while on Tarceva (+/- 7 days), and/or one month post last dose of Tarceva (+/- 7 days). Patients on Tarceva, who are unable to return for their follow up visits and 1 month post last dose of Tarceva visit, will be contacted by the research nurse by phone to review/asses the following; Update of medical history, assessment of AE's concurrent medications. They will return their unused Tarceva medication along with their medication diaries to the research nurse via mail.

g= All adverse events will be collected until 30 days after the last study dose of Tarceva or 30 days post RT visit (whichever is last), then only neurocognitive decline will be captured.
h = Only if patient has abnormal values during initial screening testing
i= within 7 days of starting protocol treatment
j= weekly until stable
k= Prior to radiation
l = During last week of radiation therapy (+/- 7 days)
m= every 3 months (+/- 14 days) for 2 years then every 6 months after
n= patients with deteriorating conditions who are unable to return may be followed up by telephone. MRI brain, physical exam, mini-mental exam, QOL Index and neurocognitive testing may be excluded.
o= for patients with progressive CNS disease we will record survival only.
p= Optional neurocognitive tests will include Digit Span, Digit Symbol, Hopkins Verbal Learning Test, Controlled Oral World Association, Trail Making Test Part A, Trail Making Test Part B, Grooved Pegboard, Barthel ADL Index, M.D. Anderson Symptom Inventory, and Functional Assessment of Cancer Therapy with Brain Module. As of July 18, 2012- Optional tests will no longer be completed.

6.1 Concomitant Medications

The Investigator will be permitted to prescribe treatment(s) at his or her discretion, which must be recorded on the Case Report Form (CRF). All concomitant meds will be tracked until 1 month post last dose of Tarceva.

6.2 Study Discontinuation

Once enrolled in this study, patients will be allowed to discontinue Tarceva at anytime during this study, before, during or after radiation and be considered“off active treatment’. If for any reason a patient wishes to discontinue taking Tarceva they will be allowed to do so. Patients will also be allowed to stop radiation at anytime as well; however, doing so will preclude them from continuing to receive Tarceva. Patients will be allowed to have a drug break of up to seven days: however, longer breaks may lead to removal from the study based on the discretion of principal investigator. Additionally the principle investigator may choose to discontinue a patient at any time. All reasons for discontinuation of treatment must be documented. Patients will be considered “on active treatment” while they are taking Tarceva. Once Tarceva is stopped patients will be defined as “off active treatment” and will still undergo routine follow up and screening as per the study calendar (see section 6.0). If after disease progression the patient’s treating physician feels it is in the best interest of the patient to continue Tarceva, they may do so and the patient may also receive other therapies while continuing the study drug Tarceva without having the patient terminated from the study. Monitoring and follow up will continue as per the study calendar (see section 6.0).

6.3 Efficacy Evaluations

MRI, or CT, Spitzer Quality of Life Index (Appendix E), Folstein Mini-Mental Status Exam (Appendix F) will be done every three months. As of 2-14-13, MMSE and Spitzer QOL evaluations will no longer be completed.

6.3.1 Optional Neurocognitive tests: As of July 18, 2012, we will no longer be completing optional neurocognitive testing.

The characteristics of a clinical trial battery to assess cognitive function, symptoms, and QOL must include the following: (20) brief ,i.e., able to be completed within 45 minutes by most patients, including those feeling ill, (21) sensitive to changes in patient function with results uninfluenced by prior exposure to the tests ,and (22) inexpensive. We have developed such a battery; the time to complete the cognitive assessment is on average 23 minutes and we have demonstrated that the assessment is practical in terms of cost and burden to patient, and is insensitive to repeated administration (20).

Neuropsychological assessments will be conducted prior to treatment and at designated intervals. Based on similar studies, we anticipate that more than 90% of patients will be willing to participate. Patients who have progressive disease will be followed as long as they are receiving treatment for their disease. At each time point, the test battery described below will be repeated and correlative studies will be obtained.

The following tests were selected because they are widely-used standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in other clinical trials. The tests have published normative data that takes into account age, and where appropriate, education and gender. The tests were also selected to minimize the effects of repeated administration. Data obtained on other studies reveals that patients tend to perform normally on tests of attention span, reflecting adequate effort is being put forth, and that mood disturbance does not correlate with the results of the cognitive portion of the battery. The memory test has six alternate forms. The other tests measure motor and information processing speed and are relatively resistant to the effects of practice. The total time for test administration, including the QOL and symptom measures, is less than 40 minutes.

Cognitive Function	Test
Attention span	Digit Span (21)

Graphomotor speed	Digit Symbol (21)
Memory	Hopkins Verbal Learning Test (22)
Verbal fluency	Controlled Oral Word Association (23)
Visual-motor speed	Trail Making Test Part A (24)
Executive Function	Trail Making Test Part B (24)
Motor dexterity	Grooved Pegboard (24)

Symptoms

Activities of daily living	Barthel ADL Index (25)
Symptoms	M.D. Anderson Symptom Inventory (26)

QOL

Quality of life	Functional Assessment of Cancer Therapy with Brain Module (27)

Statistical Considerations

We will determine the difference between the pre-treatment baseline and follow-up assessment scores by the reliable change (RC) index (28). This index is derived from the standard error of measurement (SEM) for each test in the battery. One advantage of this statistic is that the baseline level of performance of a given individual is accounted for, since these values may vary from patient to patient.

The SEM is calculated from the test-retest reliability (r) and the standard deviation of test scores (SD): $SEM=SD(1-r)^{½}$. The standard error of difference is then calculated: $SE_{diff}=[2(SEM^2)]^{½}$. A reliable change (RC) in test scores from baseline to follow-up is considered significant if it falls within a 90% confidence interval that does include zero. For each subject the difference between the pre-treatment baseline and each follow-up assessment will be coded (according to the RC index) as 1 (deterioration), 2 (no change), and 3 (improved). Cross tabulations between this variable, time, and possibly treatment group (to account for multi-arm studies) will be used to examine the percentages of patients in each treatment group that show meaningful losses or gains in the various test domains over the course of the study.

One disadvantage of using the RC approach, however, is that the magnitude of change is not captured. Therefore, we plan to supplement our repeated measures analysis using raw scores.

6.4 Dose Modification / Toxicity Management

Anti-diarrheal and anti-rash medications may be introduced if clinically indicated. Previous Phase I and II studies have demonstrated the frequency and severity of diarrhea can be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea resolves for 12 hours.

Skin rash or dermatosis has been observed during the first several days of treatment with Tarceva in many patients and has been noted to diminish in severity despite continued treatment. No controlled clinical trials have been conducted to allow definitive recommendations on the treatment of Tarceva -related rash.

Patients who develop a rash characterized by pustules or raised red areas may be treated with oral minocycline (100 mg BID for 7 – 10 days to a maximum of 150 mg BID for 7 – 10 days as clinically indicated) at the discretion of the Investigator. Minocycline is known to interfere with anticoagulants and oral contraceptives. Patients treated with minocycline who are taking anticoagulants and/or oral contraceptives will be instructed to use a second barrier contraceptive while on Minocycline and should be monitored accordingly.

Dose adjustments may be made for toxicity and are to be made based on the greatest degree of toxicity. The initial dose reduction is from 150 mg/day to 100 mg/day. If significant toxicity is still apparent, the dose may be reduced a second time to 50 mg/day. Significant toxicity will be defined as any grade 3 or 4 toxicity that the patient find unbearable. Any patient who fails to tolerate treatment of 50 mg/day will be allowed to have a drug holiday for up to 7 days. Any patient requiring a treatment break longer than seven days may be withdrawn from the study based on the discretion of the principal investigator. Patients may resume drug or increase a previously decrease dosage based on the discretion of their medical oncologist. For analysis and monitoring patients on any dose of drug will be considered “on active treatment”.

Tarceva dosing should be discontinued for any grade 3 or greater toxicity that does not respond to treatment or failure to recover from hematological toxicity within 14 days.

For patients that are off Tarceva for more than 30 days the only toxicities that will be reported and recorded in PDMS will be neurocognitive decline.

7.0 Radiation Therapy

Radiation therapy will be given once per day, five days a week for 14 days. Radiation will be given at a dose of 250 cGy per day for 14 fractions for a total dose of 3500 cGy. Radiation will be delivered with 6MV photons using opposed lateral beams dosed to mid plane.

8.0 Adverse Events

All adverse events will be graded according to NCI CTC version 3.0

> Adverse drug experience means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action (21 CFR 314.80).

An adverse event is any adverse change from the subject's baseline condition, including any clinically significant laboratory test value abnormality that occurs during the course of the clinical study after the informed consent is signed, whether the adverse event is considered related to the treatment or not.

All adverse events will be collected until one month post last day of Tarceva or radiation (whichever is last). This may require obtaining clinical blood samples for appropriate laboratory tests until their values return to baseline levels or performing follow-up physical examinations until resolution of identified abnormalities.

The most common adverse reactions in patients receiving single-agent TARCEVA 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

	TARCEVA 150 mg N = 485			Placebo N = 242		
NCI CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Rare, But Serious

In some patients taking erlotinib and oral blood thinners INR have been reported abnormally elevated. The elevation of INR was associated with bleeding.

- Some patients (less than 1%) taking erlotinib can get 'interstitial lung disorder' or 'interstitial pneumonia'. This can cause worsening of existing lung problems or causes new lung problems, such as sudden onset of shortness of breath, fever, cough, and/or problems

with oxygen getting through the lungs to the blood. In some patients, this lung disease has been fatal.

- Inflammation of the lung, pulmonary fibrosis (scarring), and lung infiltrates may occur in patients on erlotinib.
- Eye changes and blurred vision and corneal (lining of the eye) damage
- Stroke
- Blood clots
- Weight loss
- Confusion
- Heart attack

Serious side effects of erlotinib are infrequent. They are usually not severe enough to require discontinuing treatment.
PDMS Recording Requirements

AE's will be recorded according to Phase II protocols.

Recommended Adverse Event Recording (PDMS) Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.1 Severity of Adverse Drug Experiences

Adverse drug experiences will be graded according to the criteria in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

(Appendix B). The toxicity criteria can be accessed through the NCI website (ctep.cancer.gov/reporting/ctc.html).

Clinical adverse events not classified by this scale will be categorized using the following definitions:

MILD	discomfort noted, but no disruption of normal daily activity
MODERATE	discomfort noted of sufficient severity to reduce or adversely affect normal activity
SEVERE	incapacitating, with inability to work or perform normal daily activity

8.2 Serious Adverse Event Reporting (SAE)

A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above may also be considered serious adverse events. Any important medical event can and should be reported as an

SAE if deemed appropriate by the Principal Investigator or MDACC- Office of Research Education and Regulatory Management (ORERM).

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to ORERM, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in ORERM.

- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to ORERM.

- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of study treatment. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to ORERM. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by MDACC (Safety Project Manager ORERM) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, MDACC's guidelines, and Institutional Review Board policy.

8.3 Investigator Communication with Supporting Companies

The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for all SAEs, and all SAEs will be faxed (within 24 hours of learning of the event) to:

OSI Drug Safety
Fax number: 303-546-7706

9.0 Data Collection, Study Monitoring, and Data Disclosure

9.1 Data Collection and Reporting
Data for each patient will be recorded in PDMS.

10. Administrative Considerations

10.1 Patient Registration Procedure
All subjects will be registered in Clinical Oncology Research System (CORe).

11.0 Statistical Consideration
Phase II study of 20 patients (40 in total when combined with the Arizona study) to determine the effect of combining whole brain radiation with Tarceva. From what has been observed from the initial 15 patients enrolled at the Arizona Cancer Center, we would expect the vast majority of patients, to be in recursive partitioning analysis (RPA) class II, with the remaining falling into class I and a small percentage in class III. From the first 15 patients enrolled 4 remain alive, of the patients that passed away the median survival has been 9.5 months, while the RPA predicted survival was 4.2 months. While the initial result from the Arizona study are encouraging accrual has been longer than expected, which is why we have proposed to open a similar study here at MD Anderson. If this initial phase II study is successful it will serve as the foundation for a much larger multi-institutional phase III study.

11.1 Study Endpoints
Primary Endpoint:
Median survival

11.2 Background
The primary objective of this study is to estimate the median survival of patients with brain metastases from non-small cell lung cancer treated with Tarceva combined with whole brain radiation therapy.

Gaspar et al. provides a definition of average survival for patients with brain metastases stratified into three classes based on age, KPS and control of primary disease. This information came from an analysis of 1200 patients from three earlier RTOG trials. Based on this study one can expect the following survival. (9)

Class 1 patients with KPS >70 and age <65yrs to live approximately 7.1 months
Class 2 patients not meeting Class 1 or 3 criteria, have an average survival of 4.2 months
Class 3 patients with KPS < 70 have an average survival of 2.3 months

This study will be conducted in parallel with an identical study at the University of Arizona that was started on March of 2006. So far this study has accrued 15 of 20 patients, as of 8/2008. From these initial 15 patients the vast majority fall into RPA class II, with the reaming falling into class I and a small percentage in class III. From the first 15 patients enrolled the 4 remain alive, of the patient that have passed away the median survival has been 9.5 months, while the RPA predicted survival was 4.2 months.

The data from the Arizona study will be combined with this study (based at MD Anderson) which will accrue an additional 20 patients, producing a total of 40 patients for analysis. Patients will be analyzed based on the intent-to-treat principle. We will also analyze the subset of evaluable patients. Evaluable patients are defined as those patients that have completed WBRT and Tarceva.

11.3 Sample Size

We assume that the true median survival for the historical control is 4.2 months (averaging to the historical value for class 2), and we assume that the true median survival will be increased by 43% to 6.0 months with this therapeutic approach. This represents a hazard ratio (experimental/historical) of 0.70. We assume uniform accrual over 24 months, an additional follow-up period of 9 months, exponentially distributed death times. The exponential MLE test for a single arm study at the one-sided 0.10 significance level will yield 80% power to detect an increase in median survival from 4.2 to 6 months with a sample size of 40 patients.

11.4 Patient Accrual

MD Anderson treated 250 patients with all forms of brain metastasis in 2007 alone, given that approximately 60% of all brain metastasis are derived from NSCLC we would expect about 150 cases to be attributed to NSCLC, which would result in 12.5 patients per month, as such an estimated accrual of 4-6 pts per month would lead to a completion time of 3-5 months.

11.5 Data Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients overall and by treating institution.

11.5.1 Endpoint Analysis

11.5.1.1 Survival

We will use the product limit estimator of Kaplan and Meier (1958) to estimate the overall survival of all patients using the intent-to-treat principle. We will report the median survival and its associated 95% confidence interval.

We will also estimate overall survival stratified by treating institution and class, as described above in section 11.2.

We will compare the estimates of survival from this study with a recent reported phase III randomized RTOG trial, 0118, which randomized 332 patients to WBRT with or without Thalidomide (19). Our patients will be compared to both the overall survival and CNS progression free survival from this study.

We will tabulate cause of death by treating institution and by class, and we will compare the cause of death for patients in this study with patients from RTOG 01188.

We will analyze progression-free survival (PFS) in the same manner as overall survival.

We will use the methods described in Klein and Moeschberger (1997) to test for differences in survival between the matched pairs. To help us understand how similar/dissimilar patients from MDACC and Arizona are we will summarize the demographic and clinical characteristics of these patients separately. We will also estimate the survival of the 40 patients (20 from MDACC and 20 from AZCC) with the product-limit estimator of Kaplan and Meier (1958) stratified by study center (MDACC, AZCC), and we will use Cox (1972) proportional hazards regression to model survival of these 40 patients as a function of study center and estimate the hazard ratio (MDACC:AZCC) with a 95% confidence interval. For the match control based variables we will use patients from a prior randomized whole brain radiation therapy (WBRT) study performed by the Radiation Therapy Oncology Group (RTOG) study (RTOG 0118). Patients will be matched based on age, KPS, number of brain metastasis and control of systemic disease. If there is more than one match available for a patient we will review all cases.

11.5.1.2 Quality of Life

We will use descriptive statistics to summarize the scores on the Spitzer Quality of Life Index (SQLI) and the Folstein Mini-Mental Status Exam (FMMSE) at baseline, at the end of Radiation Therapy, monthly while on Tarceva and/or one month post last dose of Tarceva, and then once every 3 months. For patients who are unable to return for their monthly research nurse visit and their 1 month post last dose Tarceva visit, the Spitzer Quality of Life index and Folstein Mini-mental exam (with exception to the last four questions) will be conducted by the research nurse monthly over the phone. We will summarize these scores by class and by treating institution as well. We will similarly summarize the change from baseline in scores of the SQLI and the FMMSE. We will use mixed effects regression to model changes in SQLI and FMMSE over time with patient as a random effect and treating institution and class as fixed effects with a spatial variance-covariance structure.

11.5.1.3 Mutational Analysis

Tumor tissue will be acquired from the source used to establish the diagnosis of malignancy. The EGFR receptor will be sequenced and evaluated for small deletions that affect amino acids 747 through 750 or point mutations, with the most commonly implicated replacement being of leucine by arginine at codon 858 [L858R] (18). If the patient goes on to have their metastatic brain lesion surgically resected, we will also plan to evaluate protein level of other key mediators implicated in the EGFR pathway. Protein analysis will be carried out with western blots and/or immunohistochemistry techniques, proteins analyzed will include EGFR, p-AKT, PTEN, Vimentin, Fibronectin and E-Cadherin.

11.5.2 Interim Reports

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. The reports contain:
a) the patient accrual rate with a projected accrual completion date
b) the pretreatment characteristics of accrued patients
c) the frequency and severity of toxicities
d) the results of any completed study chair modality reviews

12.0 References

(1)
Jemal, A, Tiwari, RC, Murray, T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004; 54:8.

(2)
Parkin, DM, Pisani, P, Perlay, J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer 1993; 54:594.

(3)

Pisani, P, Parkin, DM, Ferlay, J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden.
Int J Cancer 1993; 55:891.

(4)
Peto, R, Lopez, AD, Boreham, J, et al. Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. Lancet 1992; 339:1268.

(5)
Patchell, R. Brain metastases. Handbook of Neurology 1997; 25:135.

(6)
Posner, JB. Management of brain metastases. Rev Neurol (Paris) 1992; 148:477.

(7)
Sawaya, R, Bindal, RK. Metastatic brain tumors. In: Brain Tumors, Kaye, AH, Laws, ER (Eds), Churchill Livingstone, Edinburgh 1995. p.923.

(8)
Kaye Andrew Et al. Brain tumors: An Encyclopedic Approach
Churchill Livingstone 1997

(9)
Dancey, et al. Targeting Epidermal growth Factor receptor—are we missing the mark
Lancet 2003 July 5; 362(9377):62-4

(10)
F.G Baker 2nd, et al. EGFR overexpression and radiation responses in Glioblastoma multiforme
Int J. Radiat. Oncol. Biol. Phys. 51 (2001) 410-418

(11)
Fuster LM, Sandler AB. Select clinical trials of Erlotinib (OSI-774) in non-small-cell lung cancer with emphasis on phase III outcomes. Clin Lung Cancer. 2004 Dec;6 Suppl 1:S24-9.

(12)
Proceedings of the 11th NCI · EORTC · AACR Symposium 380 Oral administration of the specific EGFR tyrosine kinase inhibitor, ZD1839 (Iressa TM), is active against EGFR-overexpressing intracranial tumors. AB Heimberger, GE Archer, RE McLendon, D Price, AH Friedman, HS Friedman, DD Bigner, JH Sampson. *Duke University Medical Center, Durham, NC, USA*

(13)
Stea Baldassarre et al, Time and dose-dependent radiosensitization of the Glioblastoma multiforme U251 cells by the EGF receptor tyrosine Kinase inhibitor ZD1839
Cancer Letters 202 (2003) 43-51

(14)
Bonner JA et al, Cetuximab prolongs survival in patients with locoregional advanced squamous cell carcinoma of the head and neck: A phase III study of high dose addition therapy with or without cetuximab. Journal of Clinical Oncology 2004, July 15:22 (14S) abstract 5507

(15)
S. Krishman, P Brown, K Ballman, J Fiveash, J Uhm, C Giannini, F Geoffrey, J Bucker
Phase I trial of Erlotinib with radiation therapy (RT) in patients with glioblastoma multiforme.
ASCO abstract #1513
http://www.asco.org/ac/1,1003,_12-002643-00_18-0034-00_19-0030601,00.asp

(16)
Laurie Gaspar MD et al. Recursive Partitioning Analysis (RPA) of Prognostic Factors in Three Radiation Therapy Oncology Group (RTOG) Brain Metastases Trials. Int J Radiat Oncol Biol Phys Vol 37, No 4 pp745-751, 1997

(17)
Park JO, Lee SI, Song SY, Kim K, Kim WS, Jung CW, Park YS, Im YH, Kang WK, Lee MH, Lee KS, Park K. Measuring response in solid tumors: comparison of RECIST and WHO response criteria. Jpn J Clin Oncol. 2003 Oct:33(10):533-7

(18)
Susumu Kobayashi, M.D., Ph.D., Titus J. Boggon, Ph.D., Tajhal Dayaram, B.A.,
Pasi A. Jänne, M.D., Ph.D., Olivier Kocher, M.D., Ph.D.,
Matthew Meyerson, M.D., Ph.D., Bruce E. Johnson, M.D.,
Michael J. Eck, M.D., Ph.D., Daniel G. Tenen, M.D., and Balázs Halmos, M.D.
EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib
N Engl J Med 2005; 352:786-792, Feb 24, 2005

(19)
Jonathan P. S. Knisely, M.D., F.R.C.P.C., Brian Berkey, M.S. et al, A phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases (RTOG 0118). Int J Radiat Oncol Biol Phys Vol 71, No 1 pp79-86

(20)
Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, Kunkler I, Caudrelier J-M, Eisenberg PD, Meerwaldt J, Siemers R, Carrie C, Gaspar LE, Curran W, Phan S-C, Miller RA, Renschler MF. Neurocognitive function and progression in patients with brain metastases treated with whole brain radiation and motexafin gadolinium: Results of a randomized phase III trial. J Clin Oncol, 22:157-165, 2004.

(21)

Wechsler D: Wechsler Adult Intelligence Scale-III. San Antonio: The Psychological Corp., 1997.

(22)
Benedict RHB, Schretlen D, Groninger L, Brandt J: Hopkins Verbal Learning Test - Revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychologist 12:43-55, 1998.

(23)
Benton AL, Hamsher KdeS: Multilingual Aphasia Examination. Iowa City, IA: AJA Associates, 1989.

(24)
Lezak MD, Howieson DB, Loring DW: Neuropsychological Assessment. New York: Oxford University Press, 2004.

(25)
Wade DT: Measurement in Neurological Rehabilitation. New York: Oxford University Press, 1992.

(26)
Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle M, Morrissey M, Engstrom MC. Assessing symptom distress in cancer: The M. D. Anderson Symptom Inventory. Cancer 89:1634-46, 2000.

(27)
Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The functional assessment of cancer therapy (FACT) scale: development of a brain subscale and revalidation of the FACT-G in the brain tumor population. *Cancer* 75:1151-1161, 1995.

(28)
Jacobson NS, Truax P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 59:12-19, 1991.