For Protocol Amendment 10 of RTOG 1119, Phase II Randomized Study of Whole Brain Radiotherapy/Stereotactic Radiosurgery in Combination With Concurrent Lapatinib In Patients With Brain Metastasis From HER2-Positive Breast Cancer- A COLLABORATIVE STUDY OF NRG Oncology AND KROG.

NCI/Local Protocol #: RTOG-1119/RTOG 1119
NCI Protocol Version Date: April 2, 2019

Section	Change
Document Footer	The protocol version date was updated.
Document History table	This amendment was added.
Title Pages	Dr. Daniel Boulter's contact information has been updated. Dr. Jennifer De Los Santos's contact information has been updated
CTSU Contact Information table	Updated per current NCTN/CTSU standard text.
7.2	Due to a Request for Amendment (RA) from CTEP for studies using Lapatinib the Comprehensive Adverse Events and Potential Risks (CAEPR) list for lapatinib was updated. As part of the implementation of version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE), the CAEPR list for lapatinib, which was previously in CTCAE 4.0 language (version 2.7), has been migrated to CTCAE 5.0 language (version 2.8). **There is no new or modified risk information for Lapatinib.**
7.6	The last two paragraphs were removed due to redundancy with Section 7.7 and to adhere to current NRG Oncology standard language.
10.3	This section is deleted as the reimbursement information is posted on the CTSU website; the remainder of this section was renumbered accordingly.

NRG ONCOLOGY

RTOG 1119

PHASE II RANDOMIZED STUDY OF WHOLE BRAIN RADIOTHERAPY/STEREOTACTIC RADIOSURGERY IN COMBINATION WITH CONCURRENT LAPATINIB IN PATIENTS WITH BRAIN METASTASIS FROM HER2-POSITIVE BREAST CANCER - A COLLABORATIVE STUDY OF NRG ONCOLOGY AND KROG

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation, Inc., and SWOG

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Lapatinib	NCI/PMB	727989	70252	NCI/DCTD

PHASE II RANDOMIZED STUDY OF WHOLE BRAIN RADIOTHERAPY/STEREOTACTIC RADIOSURGERY IN COMBINATION WITH CONCURRENT LAPATINIB IN PATIENTS WITH BRAIN METASTASIS FROM HER2-POSITIVE BREAST CANCER - A COLLABORATIVE STUDY OF NRG ONCOLOGY AND KROG

Document History

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Amendment 10	**April 2, 2019**	**N/A**
Amendment 9	February 14, 2018	N/A
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PHASE II RANDOMIZED STUDY OF WHOLE BRAIN RADIOTHERAPY/STEREOTACTIC RADIOSURGERY IN COMBINATION WITH CONCURRENT LAPATINIB IN PATIENTS WITH BRAIN METASTASIS FROM HER2-POSITIVE BREAST CANCER - A COLLABORATIVE STUDY OF NRG ONCOLOGY AND KROG

<table>
<tr><th colspan="3">CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (02-APR- 2019)</th></tr>
<tr><th>To submit registration documents:</th><th>For patient enrollments:</th><th>Submit study data</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.

Regulatory Submission Portal:
(Sign in at www.ctsu.org,
and select the Regulatory Submission sub-tab under the Regulatory tab.)

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

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com</td><td>Submit study data to:
NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103

Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org

Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3"><u>For patient eligibility or treatment-related questions</u> Contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
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</table>

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PHASE II RANDOMIZED STUDY OF WHOLE BRAIN RADIOTHERAPY/STEREOTACTIC RADIOSURGERY IN COMBINATION WITH CONCURRENT LAPATINIB IN PATIENTS WITH BRAIN METASTASIS FROM HER2-POSITIVE BREAST CANCER – A COLLABORATIVE STUDY OF NRG Oncology AND KROG

SCHEMA (7/22/16)

STRATIFY	Graded Prognostic Assessment (GPA) Score: 1.5-2 vs. 2.5-3 vs. 3.5-4 Use of Non-CNS–Penetrating HER2 Blockade at Study Entry: No vs. Yes: trastuzumab ± pertuzumab RT to Be Used: WBRT vs SRS	**RANDOMIZE**	**Arm A** Radiation (WBRT or SRS) Versus **Arm B** Radiation (WBRT or SRS) Plus Lapatinib

See Section 6.0 for details of radiation therapy and Section 7.0 for details of drug therapy.

Patient Population: (See Section 3.0 for Eligibility) (08-FEB-2018)
Pathologically (histologically or cytologically) proven diagnosis of invasive HER2-overexpressing breast cancer (3+ staining by immunohistochemistry or HER2 gene amplification by FISH or SISH ≥ 2.0). At least one measurable, , unirradiated parenchymal brain lesion (See Section 3.1 for details).

Required Sample Size: 143

ELIGIBILITY CHECKLIST (08-FEB-2018)
(page 1 of 4)

NRG Oncology Institution #
RTOG 1119
Case #

_____(Y) 1. Does the patient have pathologically (histologically or cytologically) proven diagnosis of invasive breast cancer?

_____(Y) 2. Is the breast cancer HER2 overexpressing (3+ staining by immunohistochemistry or HER2 gene amplification by FISH or SISH ≥ 2.0)?

_____(Y) 3. Does the patient have at least 1 measurable, , unirradiated parenchymal brain metastasis per section 3.1.3. (For a single solitary lesion the size must be ≥ 10 mm; for 2 or more lesions, the size of at least 2 lesions must be ≥ 5mm) within 21 days prior to study entry?

_____(Y/N) 4. Does the patient have progressive parenchymal brain metastases following stereotactic radiosurgery for 1-3 brain metastases, with at least 1 new measurable brain lesion?

_____(Y/N) 5. Does the patient have progressive parenchymal brain metastases following surgical resection of 1-3 brain metastases, with at least 1 measurable brain lesion?

_____(Y) 6. Has the patient had a history/physical examination within 21 days prior to study entry?

_____(Y) 7. Is the patient's Karnofsky performance status ≥60 within 21 days prior to study entry?

_____(Y) 8. Is the patient's age ≥ 18?

_____(Y) 9. Is the patient able to swallow and retain oral medication?

_____(Y) 10. Does the patient have adequate hematologic, renal, hepatic function within 21 days prior to study entry, as defined in section 3.1.9?

_____(Y/N) 11. Is the patient a woman of childbearing potential?
_____ (Y) If yes, was there a negative serum pregnancy test within 21 days prior to study entry?
_____(Y) If yes, is the patient, if sexually active, willing to practice adequate contraception during therapy and for 12 months after protocol treatment completion?

_____(Y/N) 12. Is the patient male?
_____(Y) If yes, is the patient, if sexually active, willing to practice adequate contraception during therapy and for 12 months after protocol treatment completion?

_____(N) 13. Has the patient had prior WBRT?

_____(Y/N) 14. Has the patient had prior lapatinib therapy?
If yes, does the patient meet the prior lapatinib requirements in section 3.1?

NRG Oncology Institution #
RTOG 1119
Case #

_____(N) 15. Does the patient have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements?

_____(Y/N) 16. Has the patient had a prior invasive malignancy (except non-melanomatous skin cancer, curatively resected thyroid papillary carcinoma, and invasive and non-invasive cancers related to the breast cancer)?

_____(Y) If yes, has the patient been disease free for a minimum of 3 years?

_____(N) 17. Does the patient have leptomeningeal disease?

_____(N) 18. Has the patient had prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields except patients who have progressed following stereotactic radiosurgery for 1-3 brain metastases, with at least 1 new lesion?

_____(N) 19. Has the patient ever received prior RT(any site) with concurrent lapatinib per section 3.2?

_____(N) 20. Does the patient have any comorbidities described in section 3.2.6?

_____(N) 21. Does the patient have ≥ grade 2 rash of any cause at the time of study entry?

_____(N) 22. Does the patient have ≥ grade 2 diarrhea of any cause at the time of study entry?

The following questions will be asked at Study Registration:

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

_____ 18. Medical oncologist's name

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ 24. Graded prognostic factor (GPA)? (1.5-2 or 2.5-3 or 3.5-4)
(See Appendix IV for scoring)

_____(Y/N) 25. Use of non-CNS–penetrating HER2 blockade at study Entry (Yes = trastuzumab ± pertuzumab; No = None)

_____ 26. RT to be used (WBRT or SRS)
(1/2) (Credentialing Required for SRS)
1. WBRT (no limit on number of metastases)
2. SRS? (no more than 10 metastases permitted)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Central Nervous System (CNS) Disease in Patients With HER2-overexpressing Breast Cancer

Human epidermal growth factor receptor 2 (HER2)–positive breast cancer is a disease with distinct clinicopathological features and accounts for 25% to 30% of all invasive breast cancer. HER2-positive breast cancer is characterized by a particularly aggressive course whose natural history (Slamon 1987), however, has been dramatically improved since the introduction of trastuzumab, an anti-HER2 monoclonal antibody (Dawood 2010).

HER2 overexpression is known to be associated with an increased risk of brain metastasis both as the site of first relapse (4.3% vs. 0.4%) (Kallioniemi 1991) and of eventual relapse. Autopsy data show that the incidence for CNS metastasis in HER2-positive breast cancer is higher (up to 50%) than that in HER2-negative breast cancer patients (Aragon-Ching 2007). On the other hand, a retrospective study on 9524 patients with early breast cancer identified HER-2 positivity as a clear risk factor for development of CNS relapse (Pestalozzi 2006). However, the precise biologic mechanism for the tendency of HER2-positive cancer cells to metastasize to the CNS has not been completely elucidated.

The advent of trastuzumab has radically altered outcomes, such that patients are surviving longer and the pattern of relapse is changing (Piccart-Gebhart, 2005). Trastuzumab levels in cerebrospinal fluid are 300-fold lower than those in plasma (Pestalozzi 2000, Rusnak 2001), indicating that trastuzumab cannot cross the blood-brain barrier due to its high molecular weight (145,531 Da). The limited penetration of trastuzumab into the blood-brain barrier may contribute to the increased incidence of brain metastasis in patients with HER-2 positive breast cancer and CNS progression and is now emerging as a major clinical issue. An analysis of 523 metastatic breast cancer patients who enrolled in 2 clinical trials of first-line trastuzumab demonstrated a 10% incidence of isolated CNS progression, with a higher incidence of brain metastasis among the patients with HER2-positive breast cancer (Burstein 2004). As many as one-third of patients with HER2-positive metastatic breast cancer are now developing CNS disease despite receiving trastuzumab-based therapy (Bendell 2003, Clayton 2004, Lai 2004, Stemmler 2007, Gori 2007, Kennecke 2010). In contrast, the incidence of CNS metastasis in historical series was only 10% to 16% (Hagemeister 1980, Tsukada 1983, Patanaphan 1988). These increased incidences of CNS events reflect not only the inherent behavior of HER2-positive tumors but also improved survival in these patients, which allowed more CNS events to become clinically evident before death (Clayton 2004). In a recent 400-patient multi-institutional analysis (Sperduto 2011; Sperduto in press), 57% of newly diagnosed breast cancer patients with brain metastases (225/400) were HER-2 positive. Half of these patients died of intracranial disease progression rather than extracranial disease following initial standard therapy with WBRT or stereotactic radiosurgery (Bendell 2006). Therefore, in these patients, if CNS control can be enhanced by more effective treatment, survival could putatively be improved.

1.2. Standard Treatment for Brain Metastases

The selection of initial treatment for brain metastasis depends on the number and size of metastases and the status of systemic disease. For patients presenting with a single brain metastasis with no or stable systemic disease, surgical resection showed improved survival in 2 of 3 randomized clinical trials (Patchell 1990, Vecht 1993, Noordijk 1994). Stereotactic radiosurgery (SRS) could be a reasonable alternative to surgical resection for patients with single, small (<3 cm), asymptomatic lesions (Shaw 2000, O'Neill 2003, Varlotto 2003). In randomized trials of WBRT plus SRS versus WBRT alone, significant survival benefit was observed for patients with a single brain metastasis when SRS was added to WBRT; a clear survival benefit has not been demonstrated among patients with

2 or more brain metastases, although addition of SRS resulted in improved local tumor control, symptoms, and performance status (Andrews 2004, Kondziolka 1999).

For patients who presented with greater than 3 brain metastases or who have limited brain metastases associated with disseminated disease with poor systemic options, WBRT is the standard treatment option, although, in practice, SRS alone is also used for these patients by some physicians at some centers. WBRT has shown improvement in survival (median survival of 4-5 months) and quality of life compared to corticosteroid use alone (Lagerwaard 1999, Fokstuen 2000, Mahmoud-Ahmed 2002). In 2 series, median survival of unselected patients with HER2-positive breast cancer was 13 to 16 months, a rate comparable to the survival reported in selected patient groups who underwent resection for solitary brain metastasis. Suh et al also observed a higher overall response rate in the HER2-positive subgroup compared to that of the entire cohort of 183 patients following WBRT (37% vs. 27% at 3 months) (ASTRO proceeding 2008).

As patients with HER2-positive breast cancer live longer, CNS progression after radiation therapy is an emerging issue. Therefore, more effective treatment approaches for this group of patients is needed.

1.3 Lapatinib

Lapatinib ditosylate (GW572016/Tykerb®; GlaxoSmithKline, Research Triangle Park, NC) is a small molecule reversible inhibitor of the intracellular tyrosine kinase domain of 2 members of the HER family, HER1 (also known as epidermal growth factor receptor [EGFR]) and HER2. It has been shown to be a potent and selective inhibitor of EGFR and HER2 tyrosine kinase activity, with IC50 values of 10.2 and 9.8 nM, respectively. It has demonstrated selective growth inhibition of human cell lines, and inhibition of cell growth was correlated with inhibition of phosphorylation of Akt by lapatinib. Inhibition of EGFR by lapatinib resulted preferentially in cell growth arrest, while inhibition of HER2 led to cell growth arrest and apoptosis (Rusnak 2001). Lapatinib showed potent growth inhibition of human breast (BT474) as well as head and neck (HN5) tumor xenografts in mice. Dose response inhibition was observed, and complete inhibition of tumor growth was observed at a dose of 100 mg/kg (Xia 2002).

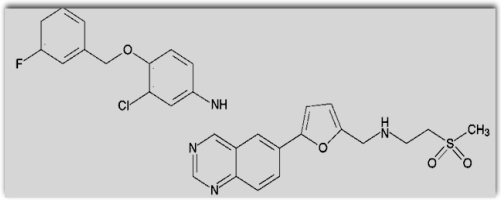

Figure 1. Chemical structure of lapatinib

1.4 Rationale for the Use of Lapatinib in the Treatment of Brain Metastasis

1.4.1 Preclinical and Translation Studies

Lapatinib has a very low molecular weight (581 Da), and its theoretical ability to cross the blood-brain barrier makes it an ideal candidate for testing against brain metastases (Nelson 2006). Preclinical evidence supports the activity of lapatinib against CNS disease. Lapatinib is the first HER2-targeting drug to be validated in a preclinical model for activity against brain metastasis from HER2-positive breast cancer (Gril 2008).

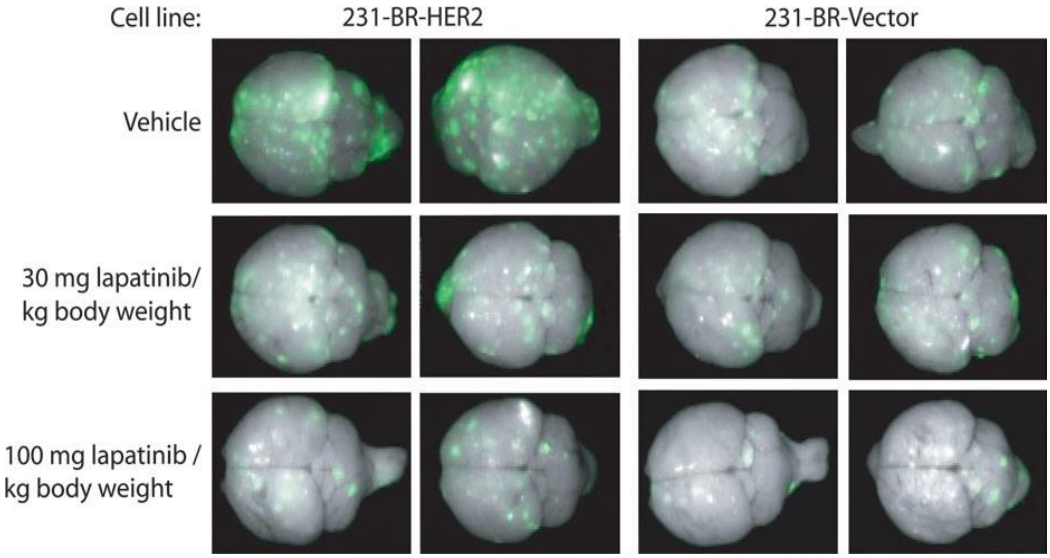

Figure 2A Lapatinib-inhibited metastatic colonization of brain-seeking HER2-positive breast carcinoma cells (231-BR-HER2) in mouse brain by 50% to 53% (Gril 2008).

In animal studies, concentrations of lapatinib were low in healthy normal brain; however, concentrations in tumor were substantially higher than the IC90 values of HER2 in BT474 xenograft models and EGFR IC50 values. In patients with glioblastoma exposed to lapatinib prior to surgery, therapeutic concentrations in tumor were observed (Kuhn 2008).

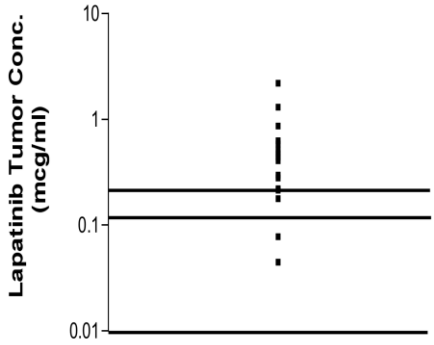

Figure 2B. Tumor concentration of lapatinib in surgical specimen of human glioblastoma in relation to IC90 inhibition in HER positive xenograft model. The 2 horizontal bars represent the IC90 range. (Kuhn 2008).

1.4.2 Clinical Studies

In an unplanned exploratory analysis of the phase III study of lapatinib plus capecitabine versus capecitabine alone, fewer CNS relapses as the site of first progression were associated with combination therapy (25% vs. 6%) (Cameron 2008). However, a recent multicenter phase II trial for patients with established CNS metastasis did not reach the predicted efficacy endpoint for lapatinib in recurrent brain metastases, although it did demonstrate modest CNS antitumor activity of lapatinib in patients who had progressive brain metastases derived from HER2-positive breast cancer despite having received prior trastuzumab and cranial radiotherapy (Lin 2008).

In a second international phase II trial, a cohort of 50 patients whose CNS disease had progressed on lapatinib monotherapy entered an extension phase involving treatment

with both lapatinib and capecitabine, obtaining an overall response rate in the brain of 20%. The study enrolled 242 patients. CNS objective responses (defined as 50% or greater volumetric regression) to lapatinib were observed in 6% of patients, and 21% of patients experienced a ≥ 20% volumetric reduction in their CNS lesions. An association was observed between volumetric reduction and improvement in progression-free survival and neurologic signs and symptoms (Lin 2009).

1.5 Rationale for Concurrent Use of Lapatinib and Radiation (7/22/16)

Lapatinib alone as therapy for CNS disease demonstrated limited potential (Lin 2009) following prior radiotherapy; however, lapatinib has been shown to have a radiosensitizing effect in vivo in a preclinical breast cancer model (Sambade 2010). At the 2010 American Society of Clinical Oncology (ASCO) annual meeting, Lin et al (2010) presented the results of a phase I study of lapatinib plus whole brain radiotherapy in patients with newly diagnosed brain metastases stemming from HER2-positive breast cancer.

1.5.1 Preclinical Evidence

HER2 Signaling and Radiosensitivity

HER2 overexpression is associated with relative radioresistance in human breast cancer cell lines (Ma 2003). No et al (2009) showed that specific inhibition of HER2 via RNA interference increased radiosensitivity of SKBR-3 breast cancer cells having HER2 overexpression; sensitizer enhancement at surviving fraction 0.5 was 1.8.

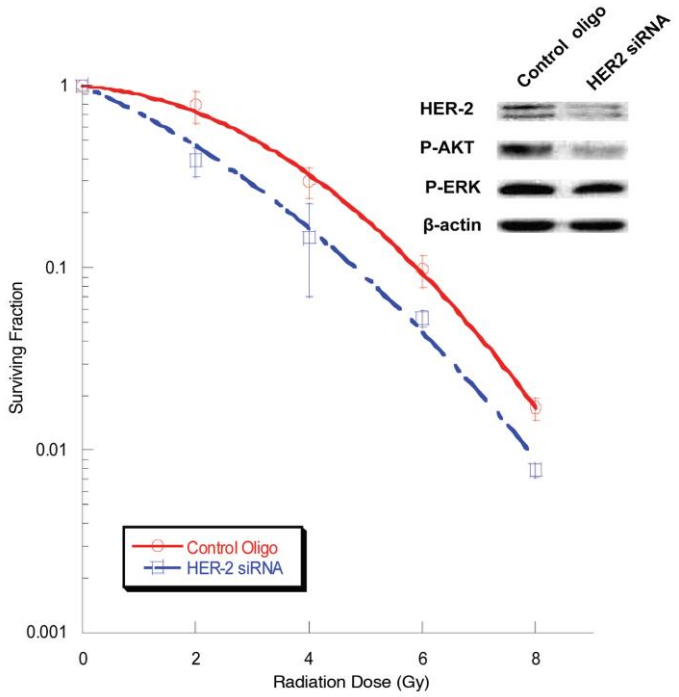

Figure 3. Specific inhibition of HER-2 using RNA interference increases radiosensitivity of SKBR3 breast carcinoma cells with activated HER-2 signaling. Specific inhibition of HER-2 using RNAi increases radiosensitivity of breast carcinoma cells with activated HER-2 signaling. SKBR3 breast carcinoma cells possessing HER-2/neu amplification were transfected with either HER-2 or nonspecific control siRNA. Specific inhibition of HER2mRNA expression using siRNA led to noticeable downregulation of HER-2 protein expression and attenuated the expression of p-AKT and p-ERK, respectively. This was associated with increased radiosensitivity of SKBR3 cells (No 2009).

In Vitro Radiosensitizing Effect of Lapatinib

Lapatinib led to inhibition of cell proliferation and enhanced the radiation-induced cell killing effect in a panel of human breast cancer cell lines that overexpress HER2 (Zhou 2004).

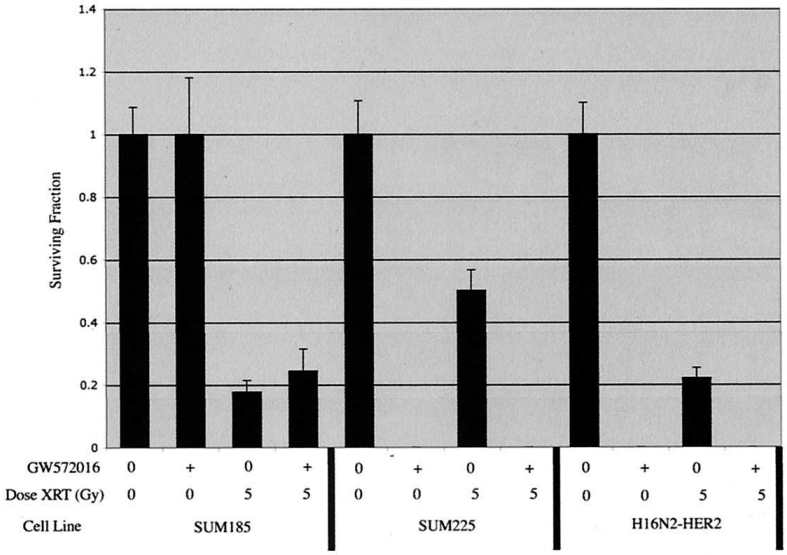

Figure 4. Radiation response of HER2 overexpressing cells with and without lapatinib (Zhou 2004)

Kim et al recently observed pretreatment of lapatinib-led downregulation of p-HER2, p-EGFR, p-AKT and p-ERK, and radiosensitized SKBR3 breast cancer cells having activated HER2 signaling (Figure 5. Kim, unpublished data).

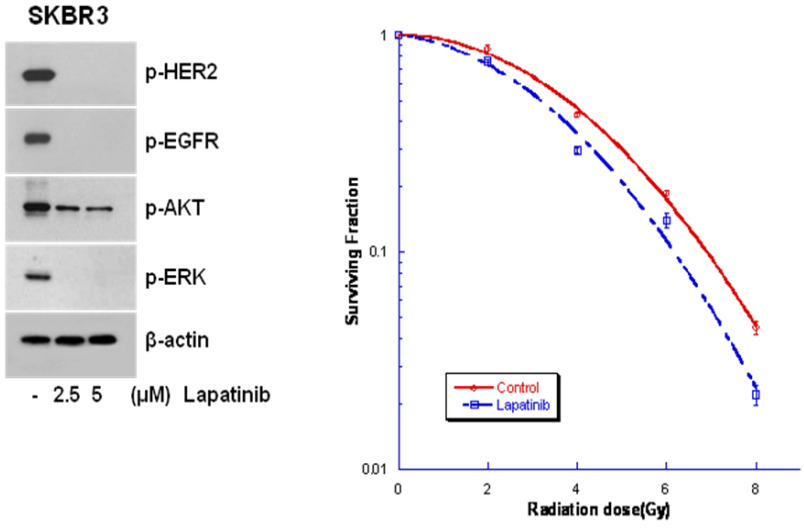

Figure 5. Lapatinib attenuated the expression of p-HER2, p-EGFR, p-AKT and p-ERK and radiosensitized SKBR3 human breast cancer cells overexpressing HER2

Lapatinib hindered the repair process of DNA double-strand breaks as measured by the γH2AX foci assay and was associated with attenuation of p-DNAPKcs, which is

known to be involved in nonhomologous end-joining repair (Figure 6A. Kim, unpublished data).

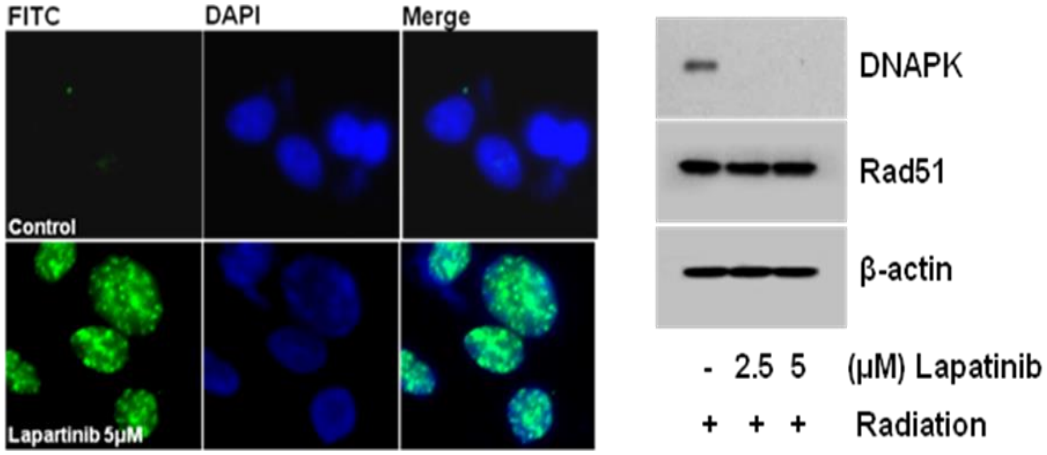

Figure 6A. Pretreatment of lapatinib-led prolongation of γH2AX foci formation 3 hours following 6 Gy of radiation and downregulated the expression of p-DNA-PKcs. (Kim, unpublished data)

Lapatinib potentiated radiation-induced apoptosis (Figure 6B) and senescence (Figure 6C).

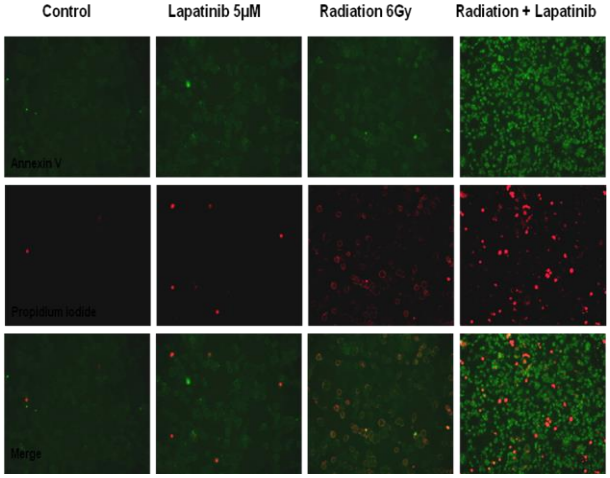

Figure 6B. Apoptosis (Kim, unpublished data)

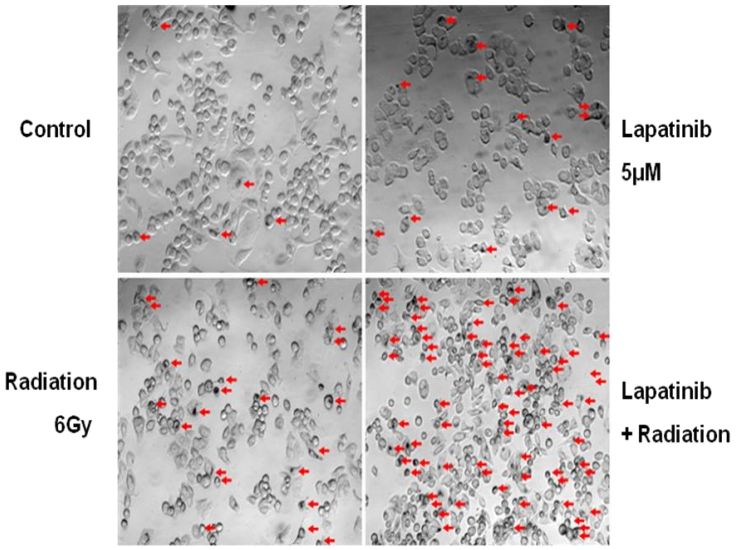

Figure 6C. Senescence (Kim, unpublished data)

In terms of the potential toxicity to the normal cell, lapatinib did not potentiate radiation-induced cell killing effect on the normal human astrocytes (Figure 7).

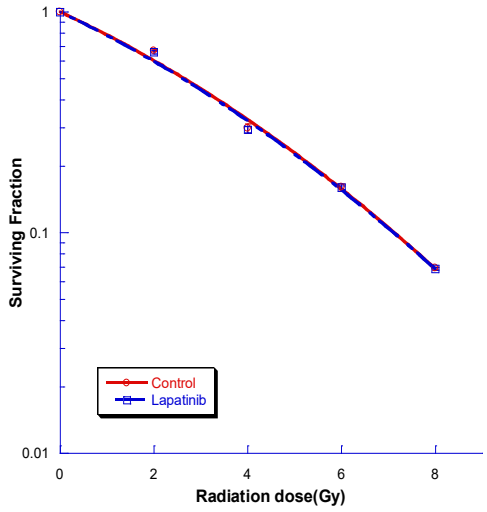

Figure 7. Lapatinib did not radiosensitize the normal human astrocytes (unpublished data).

In Vivo Radiosensitizing Effect of Lapatinib

Sambade et al (2010) showed that lapatinib potentiated tumor growth delay by radiation in human breast tumor xenografts providing the rationale for use of lapatinib as a radiosensitizer in HER2-positive breast cancer. Lapatinib and fractionated radiotherapy were given to mice with xenografts of HER2-positive SUM225 breast cancer cells. Immunohistochemical analysis confirmed that the inhibition of tumor growth was associated with alterations in ERK1 and AKT activation. The treatment with lapatinib alone to HER2-positive SUM225 breast

cancer tumors was very effective, and the treatment with both lapatinib and radiotherapy resulted in an average enhancement ratio of 1.25. The combination of lapatinib and radiotherapy was shown to be more effective in controlling the durable tumor in the HER2-positive SUM225 model compared to the treatment with either lapatinib or radiotherapy alone.

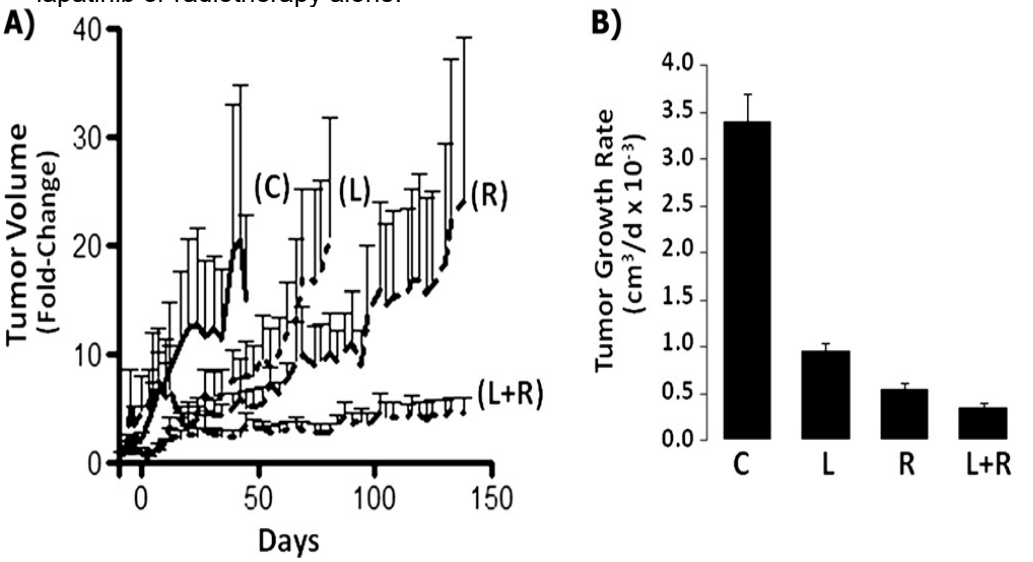

Figure 8A. Lapatinib-mediated radiosensitization of SUM225 HER2+ breast cancer xenografts. (Sambade 2010) (A) tumor volume changes normalized to baseline (Day 10) and plotted over time for each treatment group. C = vehicle control; L = lapatinib; R = radiotherapy; L+R = lapatinib plus radiotherapy. (B) Tumor growth rates = the slopes of growth curves for study duration for each treatment group

The radiosensitizing effect of lapatinib was correlated with inhibition of p-AKT in HER2+ breast cancer xenograft model (Sambade 2010).

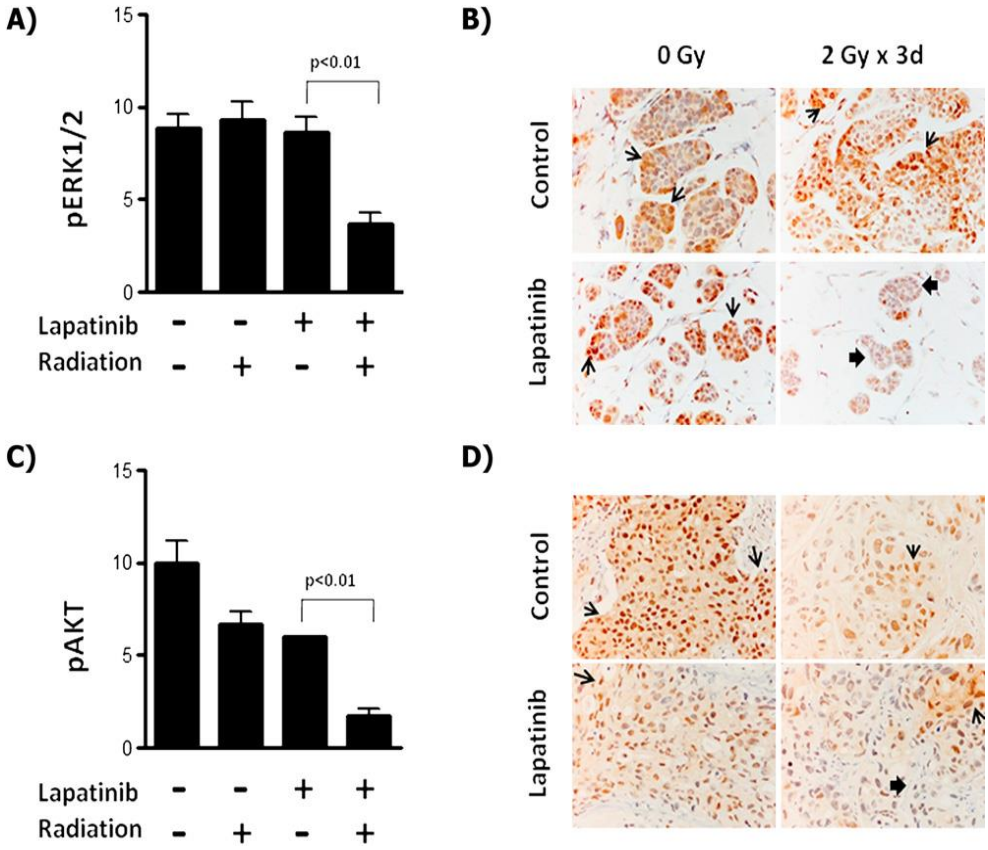

Figure 8B. The immunohistochemical study confirmed that the radiosensitization by lapatinib was relevant to AKT inhibition in the HER2+ SUM225 model (C, D).

1.5.2 Clinical Evidence

A phase I study of lapatinib in combination with WBRT in patients with brain metastases from HER2-positive breast cancer was recently reported (Lin 2010). Lapatinib 750 mg twice per day was given to patients on the first day, then 1000 mg, 1250 mg, or 1500 mg once daily was given during the first 8 days prior to WBRT (37.5 Gy in 15 fractions). The drug was given continuously throughout radiation therapy. After the WBRT treatment, 2 mg/kg of trastuzumab was given to patients every week with 1000 mg of lapatinib daily. The determination of the maximum tolerated dose (MTD), defined as the dose at which dose-limiting toxicities (DLTs) occurred in 7 days during WBRT, was the primary endpoint. Planned accrual was 27 patients at the MTD to fully evaluate the feasibility. If 3 or fewer of 27 patients had a DLT, the regimen was considered beneficial. Objective response, quality of life, and survival were used as secondary endpoints. Thirty-five patients of 35 planned patients were enrolled in the study. Of 3 patients who received lapatinib 1000 mg and 5 patients who received lapatinib 1250 mg, none had a DLT. Two patients had DLTs with grade 3 diarrhea and grade 3 rash, each associated with a lapatinib dose hold of 16 days during the first cycle at lapatinib 1500 mg. Twenty-two additional patients participated in the MTD (1250 mg) dose phase. Among them, 5 patients had a DLT with ≥ 8 weeks data (21%, 95% CI 7%-42%): 2 patients with pulmonary embolus, 1 patient with grade 3 herpes simplex rash, 1 patient with grade 3 hypoxia, and 1 patient with grade 3 hyponatremia/hypokalemia. There was no grade 3/4 neurologic toxicity. Among the 24 patients who had measurable disease with at least 8 weeks of follow-up, 20 (83%, 95% CI 63%-95%) experienced an objective CNS response by 1 month after receipt of WBRT.

Based upon the preclinical data and the results of the previous phase I study, we hypothesize that lapatinib plus WBRT can improve the intracranial disease control rate

compared to WBRT alone (according to historical data for WBRT). We therefore propose a randomized phase II trial of WBRT plus or minus concurrent lapatinib treatment in patients presenting with brain metastasis stemming from HER2-positive breast cancer.

For purposes of sample size calculation and statistical analyses in this trial, we consider the complete response (CR) rate for WBRT and SRS to be 5 and 14%, respectively. The WBRT CR rate is based on Suh et al (J Clin Oncol 2006, 24:106-114). The SRS CR rate is based on a computerized search of the medical literature in which the CR varied but the median CR rate was 14%. (Bruni 2015, Fokas 2012, Gaudy-Marqueste 2006, Hasagawa 2003, Hauswald 2015, Jani 2015, Kocher 2000,Narayana 2007, Serna 2015) The response criteria are based on the *Response Assessment in Neuro-Oncology (RANO)* group recommendations for standard response and progression criteria for the assessment of brain metastases in clinical trials. (Linn 2015).

1.6 Summary

Together, recent clinical results of lapatinib treatment for progressive brain metastases derived from HER2-positive breast cancer, the evidence of its in vivo radiosensitizing effect in a preclinical tumor model, and the results of the phase I study of lapatinib and WBRT suggest that lapatinib can be safely combined with WBRT and that this approach may provide promising clinical benefit of improved survival and quality of life by increasing intracranial tumor control in HER2-positive patients with brain metastasis.

1.7 Rationale for Collaborative Studies in the US and Korea

Breast cancer is the second most common cancer in Korean women and its incidence is increasing rapidly. The median age at diagnosis in Korean women is 45 years, which is approximately 15 years younger than that for women in the US. According to the 2003-2007 annual report of the Korean Central Cancer Registry (Ministry of Health and Welfare 2008) and the National Cancer Institute's Surveillance Epidemiology and End Results Cancer Statistics Review (Altekruse 2009), breast cancers that develop before age 35 comprised 7% of Korean cases but only 1.9% of cases in the US. According to a collaborative cDNA microarray study of Stanford University and Seoul National University using 72 samples of breast cancer and normal breast tissue, Korean breast cancer patients exhibit a high percentage of HER-2 expression and hormone receptor negativity (Han 2010). Choi et al (2003) compared the expression of HER-2 between 60 Caucasian women in the US and 60 native Korean women with early-onset (age 45 years or younger) breast carcinoma. Positive HER-2 status was observed in 47.5% of Korean women, compared with only 15.8% of Caucasian women ($p<0.001$). The high proportion of early-onset, HER2-positive cases in Korean breast cancer patients will increase the value of this collaborative trial. With the reorganization of the US Cooperative Groups, the NSABP, GOG and RTOG will be uniting into a single group, which collectively will have access to a large population of women with breast cancer, and further, both the NSABP and RTOG already have Korean member sites approved, or in process.

1.8 Rationale for Allowing Prior Use of Lapatinib (09/02/2014)

Because this trial is testing the utility of lapatinib as a radiation sensitizing agent, its use as an agent (without concurrent radiation) against the patient's systemic cancer is not expected to have an impact on its ability to act as a radiation sensitizer. We will not, however, allow patients who have received lapatinib as treatment for the patient's CNS metastases. This will be defined as the use of lapatinib at any time after the diagnosis of brain metastasis.

2.0 OBJECTIVES

2.1 Primary Objective (7/22/16)

To determine if there is a signal for an increase in complete response (CR) rate in the measurable brain metastases at 12 weeks post RT (whole brain or SRS) as determined by MRI scan of the brain, with the addition of lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2 Secondary Objectives (7/22/16)

2.2.1 To evaluate CR rate of the measurable brain metastases at 4 weeks post RT (WBRT/SRS) as determined by MRI scan of the brain, with the addition of lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2.2 To evaluate objective response rate of measurable brain metastases at 4 and 12 weeks post RT (WBRT/SRS) as determined by MRI scan of the brain, with the addition of lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2.3 To evaluate targeted lesion-specific objective response rate (CR + PR) at 4 and 12 weeks post WBRT/SRS.

2.2.4 To evaluate CNS progressive disease outside the targeted measurable disease with addition of lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2.5 To evaluate targeted lesion-specific progression at 4 and 12 weeks post WBRT/SRS

2.2.6 To evaluate treatment related adverse events when adding lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2.7 To evaluate Overall CNS complete response: Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically, when adding lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2.8 To evaluate overall CNS progressive disease (within or outside targeted measurable disease) with addition of lapatinib to WBRT/SRS compared to WBRT/SRS alone.

2.2.9 To evaluate overall survival when adding lapatinib to WBRT/SRS compared to WBRT/SRS alone.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (08-FEB-2018)

For questions concerning eligibility, please contact study data manager

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of invasive breast cancer

3.1.2 HER2 overexpressing breast cancer (3+ staining by immunohistochemistry or HER2 gene amplification by FISH or SISH ≥ 2.0)

3.1.3 At least 1 measurable unirradiated parenchymal brain metastasis within 21 days prior to study entry. Patients who are to undergo SRS must have no more than 10 brain metastases. There is no limit on number of brain metastases for WBRT. The minimum size as measured on T1-weighted gadolinium-enhanced MRI must be as follows according to the number of brain metastases:

- For a single solitary lesion the size must be ≥10 mm;
- For 2 or more lesions, the size of at least 2 of the lesions must be ≥ 5 mm

Patients may also have the following provided the size requirements above are met:

- Progressive parenchymal brain metastasis following stereotactic radiosurgery for 1-3 brain metastases, with at least 1 new measurable brain lesion
- Progressive parenchymal brain metastasis following surgical resection of 1-3 brain metastases, with at least 1 measurable brain lesion

3.1.4 History/physical examination within 21 days prior to study entry

3.1.5 Karnofsky performance status ≥ 60 within 21 days prior to study entry

3.1.6 Age ≥ 18

3.1.7 Able to swallow and retain oral medication (Note, for patients unable to swallow **tablets**, an oral suspension preparation is acceptable, per Section 7.2.10)

3.1.8 Adequate hematologic, renal, hepatic function within 21 days prior to study entry, as defined by the following:

- Absolute neutrophil count (ANC) ≥ 1,200 cells/mm3
- Platelets ≥ 70,000 cells/mm3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
- Creatinine < 1.5 times institutional upper limit of normal
- Bilirubin < 1.5 times institutional upper limit of normal
- AST and ALT ≤ 3.0 times institutional upper limit of normal with or without liver metastasis

3.1.9 Patient must provide study specific informed consent prior to study entry

3.1.10 Women of childbearing potential must have a negative serum pregnancy test within 21 days prior to study entry

3.1.11 Sexually active women of childbearing potential and sexually active men must practice adequate contraception during therapy and for 12 months after protocol treatment completion

3.1.13 Prior lapatinib is allowed as long as the last dose received was > 21 days prior to study entry and provided the patient has not received it at any time after the diagnosis of brain metastasis

3.2 Conditions for Patient Ineligibility (09/02/2014)

3.2.1 Prior WBRT

3.2.2 Prior RT (any site) with concurrent lapatinib defined as 1 or more days on which the patient received both radiation therapy and lapatinib on the same day.

3.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.4 Prior invasive malignancy (except non-melanomatous skin cancer, curatively resected thyroid papillary carcinoma, and invasive and non-invasive cancers related to the breast cancer) unless disease free for a minimum of 3 years

3.2.5 Leptomeningeal disease

3.2.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields except patients who have progressed following stereotactic radiosurgery for 1-3 brain metastases, with at least one new lesion

3.2.7 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of study entry
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of study entry
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; hepatic or biliary disease that is acute or currently active or that requires antiviral therapy (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per investigator assessment)
- History of LVEF below institutional normal unless repeated and within institutional normal range within 90 days of study entry

3.2.8 Grade 2 or greater rash of any cause at time of study entry

3.2.9 Grade 2 or greater diarrhea of any cause at time of study entry

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (09/02/2014)

Note that failure to perform any required evaluations/management may result in assessment of a protocol violation.

4.1.1 Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to treatment start. (Note: Only one pregnancy test is necessary if the negative serum pregnancy test obtained as part of Section 3.1.11 is also obtained within 7 days prior to treatment start.)

4.1.2 There must be at least 14 days between FINAL dose of prior chemotherapy and 1st day of protocol treatment with recovery of toxicities to grade 0 or 1.

5.0 REGISTRATION PROCEDURES (14-FEB-2018)

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

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

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

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

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

5.1 Regulatory Pre-Registration Requirements (02-APR-2019)

5.1.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

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

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

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

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

Requirements for RTOG 1119 site registration:

- IRB approval letter (local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.
  - .
- Credentialing documentation received from IROC Houston for this trial- See Section 5.4 for details.
- IRB/REB approved consent (Non-North American and Canadian sites only: English and native language versions*)
- ***Note**: International and Canadian Institutions (Non-North American sites must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below).

Non-English Speaking Canadian and Non-North American Institutions

Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title,

credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.1.2 Downloading Site Registration Documents:

Site registration forms may be downloaded from the RTOG 1119 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NRG Oncology link to expand, then select trial protocol # RTOG 1119
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

5.1.3 Submitting Regulatory Documents:

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103
Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

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

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

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

5.1.4 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must complete the following documents and submit them to the CTSU Regulatory Office (see Section 5.1.3).

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form,
- Research Ethics Board Attestation Form.

5.1.5 Pre-Registration Requirements FOR APPROVED KOREAN AND ISRAELI INSTITUTIONS

Please see the Regulatory Resources tab under the RTOG 1119 protocol-specific page for a list of requirements to be fulfilled prior to enrolling patients to the study.

5.2 OPEN Registration (08-FEB-2018)

5.2.1 Online Registration

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

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

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration at websupport@acr.org or call the NRG Registration Desk at 215-571-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

5.3 Digital RT Data Submission to NRG Oncology Using TRIAD (08-FEB-2018)

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an AP,

NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.

- To submit images, the site physics user must be on the site's affiliated rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://www.irocqa.org/Resources/TRIAD

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.4 In order to utilize Stereotactic Radiosurgery (SRS) with a Gamma Knife or Linear Accelerator on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the IROC Houston QA Center (IROC H) web site at http://irochouston.mdanderson.org/rpc/; select "Credentialing" and "RTOG" To determine if these requirements have already been met by your institution, select "Credentialing Status Inquiry." (7/22/16)

5.4.1 The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. The questionnaire is available on the IROC H web site, http://irochouston.mdanderson.org , under "Facility Questionnaire" at the top of the homepage.

5.4.2 An SRS phantom study with IROC Houston must be successfully completed. If an institution has previously successfully irradiated an IROC-Houston SRS phantom and their treatment equipment has not changed since the initial credentialing, the institution is not required to perform the phantom irradiation study again. However, if the institutions treatment equipment has changed significantly then they will be required to re-credential by performing the phantom irradiation study again. Instructions for requesting and irradiating the phantom are available on the IROC Houston web site at http://irochouston.mdanderson.org; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution, CTSU and NRG Operations Office of your approved credentialing.

5.4.3 Institutions utilizing frameless SRS methods must complete IGRT credentialing for boney-anatomy in addition to the SRS phantom study. The institution must complete an IGRT questionnaire found on the IROC-Houston website under "Credentialing" and must submit a set of treatment day position verification images via TRIAD. Instructions can be found on the IROC-Houston website (http://irochouston.mdanderson.org) or data along with a spreadsheet of IGRT data from two anonymized SRS patients. This must include pre-treatment images which include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (kV) x-ray)

or Orthogonal (MV or kV) 2D images. These data are submitted via TRIAD. The spreadsheet can also be uploaded to TRIAD. The spreadsheet can be found on the IROC Houston QA Center website at http://irochouston.mdanderson.org. Once the data has been submitted via TRIAD, please complete the DDSI found at http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx. If the institution has already been approved for boney-anatomy IGRT, no further IGRT credentialing is required.

6.0 RADIATION THERAPY SRS/WBRT (ARMS A AND B) (08-FEB-2018)

NOTE 1: For patients being treated by WBRT and SRS, protocol treatment must begin within 21 days after the diagnosis of brain metastasis was made by MRI.

NOTE 2: For institutions desiring to use SRS as a treatment modality, patients can only be enrolled by treating physicians and institutions that have irradiated and passed the IROC SRS Head Phantom.

NOTE 3: Institutions using frameless SRS methods or planning to use IGRT for SRS treatment will need to complete an IGRT verification study.

NOTE 4: The patient must have at least 1 unirradiated metastases as described in section 3.1.3.

- Patients who are to undergo SRS: there must be no more than 10 brain metastases.
- Patients who are to undergo WBRT: there is no limit on the number of brain metastases.

6.1 Radiation Therapy Schema (7/22/16)

Schema at the beginning of the protocol should be followed.

6.2 Treatment Technology (7/22/16)

This **protocol** requires photon treatment with nominal energies between 4 and 10MV except when Co-60 treatment units are used.

WBRT

Opposed lateral helmet fields will typically be used for this treatment modality. Individually fabricated compensators, wedges and field-within-field techniques can be used to adjust for missing tissue at the discretion of the treating physician. Inverse planned IMRT is not allowed for patients getting WBRT.

SRS

3DCRT, IMRT, VMAT, Gamma Knife, Cyberknife, and Tomotherapy are allowed for patients getting SRS.

All participating sites must have calibrations verified by OSLDs through the IROC Houston Quality Assurance Center as well as credentialing for IMRT/VMAT if those technologies are being used. . Gantry mounted linac treatments should be performed with a minimum source-axis distance of 80cm.

6.3 Immobilization and Simulation (7/22/16)

WBRT

Immobilization:

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. Patients receiving WBRT should be treated in the supine position. A head-holding device must ensure adequate immobilization during therapy and ensure reproducibility

Simulation Imaging:

A non-contrast treatment-planning CT scan of the entire head region using an axial slice thickness not exceeding 2.5mm is required. The field shape should include the entire cranial contents, with flashing beyond skin and a minimum margin of 0.75 cm on the skull base as visualized on the simulator images or portal films to account for beam penumbra and day-to-day set-up variation. The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment. A planning MRI is not required for WBRT treatment.

SRS
Immobilization:
Patient setup reproducibility must be achieved using appropriate clinical devices. Multiple isocenter techniques are permitted and should be used when the separation between the isocenter and the most distant lesion exceeds 10 cm. Framed and frameless SRS delivery methods are allowed for this protocol. IGRT is required.

Simulation Imaging:
A gadolinium contrast-enhanced spoiled gradient or axial T1-weighted and T2-weighted MRI with axial thickness not exceeding 1.5mm should be used for the planning MRI. The images should be obtained with the patient in the supine position. Immobilization devices used for CT treatment planning simulation and treatment need not be used when obtaining the MRI imaging sequences, but the patient should be positioned as close to the same orientation as the CT simulation if possible.
For SRS planning with CT images, a treatment-planning CT scan of the entire head region using an axial slice thickness not exceeding 1.5mm is required. The planning CT should be fused with the planning MRI for structure definition.

6.4 Imaging for Structure Definition, Image Registration/Fusion and Follow-up (7/22/16)

A planning MRI is not required for WBRT volume delineation or treatment planning.
MRI imaging will be required to assist in volume delineation in all patients treated with SRS

6.5 Definition of Target Volumes and Margins (7/22/16)

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

WBRT
There are no required dose target volumes for patients being treated with WBRT.

SRS
For patients treated with SRS, target names should follow the naming convention detailed in the table below. Each target will be named anatomically for the lobe of the brain along with “Left (L) or Right (R)” denoting which hemisphere the target is located. Following the name will be a number representing the order in which the target appears on the MRI as one moves from patient superior to inferior.
The GTV is defined as the enhancing metastasis on a gadolinium enhanced T1 weighted MRI scan. The PTV is defined as the defined GTV plus a symmetrical 1.0mm margin. Each GTV and PTV should have “GTV#_” and “PTV#_” respectively preceding the target name. Example names are: GTV1_Frontal_L, GTV2_Occipital_R, and GTV3_Occipital_R.

Targets	Anatomical Region or Lobe	Possible Descriptors
GTV(1-10)_ CTV(1-10)_ PTV(1-10)_	Frontal Parietal Cerebellum Temporal	_L/R

	Occipital	
	Brainstem	

Detailed Specifications

6.6 Definition of Critical Structures and Margins (7/22/16)

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" under the heading of Validation in the table below must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.
Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

For WBRT patients, critical structure contouring is recommended but not required.

Standard Name	Description	Validation (WBRT)	Validation (SRS)
Brain	Brain	**Optional**	**Optional**
BrainStem	Brain Stem	**Optional**	**Required**
OpticNerve_L	Left Optic Nerve	**Optional**	**Required**
OpticNerve_R	Right Optic Nerve	**Optional**	**Required**
Orbit_L	Left Orbit	**Optional**	**Required**
Orbit_R	Right Orbit	**Optional**	**Required**

OpticChiasm	Optic Chiasm	**Optional**	**Required**
Lens_L	Left lens	**Optional**	**Required**
Lens_R	Right Lens	**Optional**	**Required**
MotorStrip	Defined as 2cm anterior and posterior to the central gyrus	**Optional**	**Required**

Detailed Specifications

6.7 Dose Prescription (7/22/16)

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

WBRT:

One treatment of 2.5Gy will be given daily 5 days per week (15 fractions) for a total of 37.5Gy over 3 weeks. Doses are specified as the target dose to a point, which shall be the dose on the central ray at mid-separation for 2 opposed coaxial equally weighted beams. All portals should be treated during each treatment session.

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**
Brain	37.5	2.5	15

SRS:

For patients with > 1 brain metastasis, the maximum SRS dose for any lesion is 18 Gy

All doses will be delivered in a single fraction. The dose will be prescribed to the isodose surface (50%-90% [maximum = 100%]), which encompasses the margin of the metastasis, as defined by the imaging studies. The maximum dose to a point that is at least 0.03 cc within each PTV will be recorded for each patient. The reported prescription dose is defined as the dose to the periphery (defined as 99% of the volume) of the PTV as established by the SRS treatment planning software, generated dose-volume histogram (DVH). The maximum point dose would be 40 Gy when a lesion that is less than 4 cc is treated to a 20Gy dose prescribed to the 50% isodose line.

SRS Target Volume	**Dose (Gy)**	**# of fractions**

<4.0cc	20	1
4.0-14.0cc	18	1
14.1-33.0cc	15	1
>33cc	Ineligible for SRS	

6.8 Compliance criteria (7/22/16)

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. Both the Per Protocol and Variation Acceptable categories are considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria for Composite Plans

The prescription dose should be specified as the dose to the periphery of the target. Deviations from the target volume dosing table listed in section 6.7 should only be made in order to comply with dose constraints to critical structures as detailed below.

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
All SRS Targets	$D_{99\%}$(Gy)	≥Rx dose	95% of Rx dose
	D_{min}(Gy)	≥90% of Rx Dose for a volume of 0.03 cc	≥40% of Rx Dose for volume of 0.03 cc

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
BrainStem	D_{max}(Gy)	≤10	None
OpticNerve_L	D_{max}(Gy)	≤8	None
OpticNerve_R	D_{max}(Gy)	≤8	None
OpticChiasm	D_{max}(Gy)	≤8	None
Orbit_L	D_{max}(Gy)	≤8	None
Orbit_R	D_{max}(Gy)	≤8	None
MotorStrip	D_{max}(Gy)	≤15	None

Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score:

Lens_L	D_{max}(Gy)	≤2
Lens_R	D_{max}(Gy)	≤2

Delivery Compliance criteria

For SRS and WBRT care should be taken to minimize the dose to the lens and orbits.
For WBRT, the radiotherapy treatment course will be continued without interruption if possible. If the sum total of treatment interruptions exceeds 2 normally scheduled treatment days, the treatment will be considered a protocol deviation unacceptable

	Per Protocol	Variation Acceptable
Start date	Within 21 day period after the diagnosis of brain metastasis was made by MRI	
Interruptions (WBRT)	0 break days	1-2 break days

6.9 Treatment Planning Priorities and Instructions (7/22/16)

WBRT:
Three-dimensional approaches to radiotherapy planning will be used for patients treated with WBRT. There are no treatment-planning priorities.

SRS:
Three-dimensional or intensity-modulated radiotherapy approaches to radiotherapy planning can be used for patients treated with SRS. In creating and optimizing a plan priority should be placed on achieving the highest possible prescription dose to the target while keeping critical structures under their maximum dose limits.
Conformity index (CI) is defined as the ratio of the prescription isodose volume to the target volume.

$$CI = \frac{PIV}{TV}$$

Gradient index (GI) gives a measure of the rate of dose fall-off outside of the target. It is defined as the ratio between the half-prescription isodose volume to the prescription isodose volume.

$$GI = \frac{PIV_{50}}{PIV}$$

RTOG Conformity and Gradient Indexes should be kept to ≤2.0 and ≤4.0 respectively if possible.

- Primary dataset for dose calculation
For WBRT, the primary dataset for calculation should be a non-contrast treatment planning CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.
For SRS, the primary dataset for calculation can either be a non-contrast treatment planning CT or planning MRI. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density.

-Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

6.10 Patient specific QA (7/22/16)

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 4%

dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

6.11 Daily Treatment Localization/IGRT (7/22/16)

WBRT

Acquisition of verification orthogonal films or images is required. This data will not be collected but should be held by the institution and available for review if requested.

SRS

For all forms of SRS except for Gamma Knife and CyberKnife dose delivery that use their own unique built-in imaging systems, IGRT verification systems must be used. Checking the agreement of the treatment beam reference point and the IGRT imaging reference point on each day of SRS treatment is required.

IGRT credentialing is required for any facilities utilizing frameless SRS methods. NRG Oncology defines IGRT as a computer assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the Tomotherapy approach.

6.12 Case Review (7/22/16)

WBRT

There will be no case reviews

SRS

The first two cases submitted by each institution will undergo pre-treatment review except for Gamma Knife. Three business days are required to complete a pre-treatment review. The 3 days start once complete data is received. All other cases will be reviewed post treatment. The digital data should be sent within a week of treatment completion. One of the Principal Investigators and the Medical Physics Co-chair will perform ongoing remote RT Quality Assurance Review after cases enrolled have been received at IROC Philadelphia-RT.

6.13 Radiation Therapy Adverse Events (7/22/16)

Adverse events related to WBRT include both short-term and long-term side effects. Short-term side effects include fatigue, hair loss, scalp erythema/irritation, and muffled hearing. These events usually resolve 2-4 weeks after WBRT, although hair loss may be permanent. Long-term side effects may include difficulty with short-term memory. All of the above are common.

Adverse events related to SRS include both short and long-term side effects. Short term side effects may include pin-site soreness for frame-based SRS and headache which resolve within 1-2 days. Long-term side effects include radiation necrosis which may cause brain swelling months after SRS. That swelling may be subclinical (seen only on MRI), transient (bloom and wilt) or persistent. If symptomatic, steroids may be needed but should be used in the lowest dose needed to control symptoms.

6.14 Radiation Therapy Adverse Event Reporting (7/22/16)

See Section 7.6 for Adverse Event Reporting

7.0 DRUG THERAPY

Protocol treatment must begin within 21 days after the diagnosis of brain metastasis was made by MRI.

7.1 Treatment With Lapatinib (Arm B patients only) (7/22/16)

7.1.1 Dose Definition

Lapatinib 1000 mg orally once daily

7.1.2 Technique of Administration

Patients should be advised to take lapatinib on an empty stomach (ie, the dose must be taken at least 2 hours **after** the last meal **and** the patient must wait at least 1 hour after the dose before eating again). If doses are held or missed, they should be continued at the end of the course of lapatinib therapy. If the patient misses more than 14 continuous days of lapatinib for any reason, protocol treatment will be discontinued. Before starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (see "Non-Study Specific Forms" on the NRG Oncology/RTOG website, or http://www.rtog.org/LinkClick.aspx?fileticket=CrZv7t2tB1w%3d&tabid=308, for a pill diary template) to record their daily pill consumption. The investigator will check this record for compliance. The diary will be retained in the patient's record for submission to RTOG ONLY upon request (ie, diaries are not to be submitted but will be retained at the site as source documents). Patients who are non- compliant must be re-instructed in the use of the pill diary.

7.1.3 Timing of Administration

SRS patients: Lapatinib dosing will start up to 1 day before SRS and should be timed to occur approximately 3-6 hours prior to SRS.

WBRT patients: On days when patients are receiving radiation treatments, lapatinib dosing should be timed to occur approximately 3-6 hours prior to WBRT.

7.1.4 Duration of Treatment

All patients randomized to receive lapatinib will take drug for 6 weeks.

SRS patients: Lapatinib will start up to 1 day before SRS and should be taken continuously for 6 weeks.

WBRT patients: Lapatinib will start up to 1 day before the first day of WBRT and continue throughout WBRT and 21 days after the final day of WBRT without drug holiday (i.e., Saturdays and Sundays included). Drug should be taken continuously including days on which WBRT is not given.

7.2 Lapatinib Agent Information (NSC # 727989, IND # 70252) (02-APR-2019)

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure for comprehensive pharmacologic and safety information

7.2.1 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

7.2.2 Chemical Name

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

7.2.3 Other Names

GW572016F, lapatinib ditosylate, Tykerb®

7.2.4 Molecular Formula

C29H26ClFN4O4S (C7H8O3S)2H2O

7.2.5 Molecular Weight

943.48

7.2.6 Approximate solubility

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

7.2.7 How supplied

GlaxoSmithKline supplies and the NCI/DCTD distributes lapatinib as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. The tablets contain 405 mg of lapatinib ditosylate monohydrate, equivalent to 250 mg lapatinib free base per tablet. The tablets are packaged into HDPE bottles with child-resistant closures containing 90 tablets per container.

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

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

Drug provided free of charge as part of a research protocol must be used only for the intended study. It is the responsibility of the Investigator to ensure the provided/investigational product is only dispensed to eligible study patients

7.2.8 Storage

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

7.2.9 Stability

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

7.2.10 Route of Administration

Oral on an empty stomach (ie, the dose must be taken at least 2 hours **after** the last meal **and** the patient must wait at least 1 hour after the dose before eating again)

7.2.11 Method of Administration

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

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

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

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

7.2.12 Possible Drug Interactions

Lapatinib is extensively metabolized by CYP3A4/5 with minor contributions from CYP 2C8 and 2C19. Co-administration of lapatinib with strong or moderate CYP3A4/5 inhibitors (including grapefruit juice) and all CYP3A4/5 inducers is prohibited. Assess risk/benefit before co-administering lapatinib with weak CYP3A4/5 inhibitors. CYP3A4/5 inhibitors may decrease lapatinib metabolism (increasing levels); while CYP3A4/5 inducers may increase lapatinib metabolism (decreasing levels).

In vitro, lapatinib inhibited CYP3A4 and CYP2C8 at clinically relevant concentrations. Avoid co-administration of lapatinib with drugs that are substrates of CYP3A4 or CYP2C8

and have narrow therapeutic windows.
Lapatinib is a substrate for P-glycoprotein (Pgp) and Breast Cancer Resistance Protein (BCRP) transport proteins. Inhibitors and inducers of these transporters may affect lapatinib exposure in patients. Lapatinib is an inhibitor of Pgp, BCRP and OATP1B1 transport proteins. Use caution when dosing lapatinib concurrently with narrow-therapeutic drugs that are substrates for these transport proteins, such as digoxin or statins.

Lapatinib is highly protein bound (> 99%) to albumin and alpha-1 acid glycoprotein; therefore, use other highly protein bound concomitant medications with caution and monitor for toxicity.

Use of proton pump inhibitors prior to lapatinib administration decreased lapatinib exposure by 27% on average. Use caution when lapatinib is administered concomitantly with PPIs.

For a list of Prohibited Drug Medications, see Section 9.2

7.2.13 Adverse Events

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

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

Version 2.8, February 4, 2019[1]

Adverse Events with Possible Relationship to Lapatinib (GW572016) (CTCAE 5.0 Term) [n= 6120]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	***Left ventricular systolic dysfunction (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***

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

Adverse Events with Possible Relationship to Lapatinib (GW572016) (CTCAE 5.0 Term) [n= 6120]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dry skin		
		Erythema multiforme	
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***
	Hot flashes		

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Pericarditis; Sinus tachycardia
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dysphagia; Gastritis; Hemorrhoids; Ileus; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; GGT increased; INR increased; Lymphocyte count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperphosphatemia; Hypoalbuminemia; Hypoglycemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Flank pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Cerebrospinal fluid leakage; Depressed level of consciousness; Dizziness; Intracranial hemorrhage; Nervous system disorders - Other (altered dream pattern); Nervous system disorders - Other (sleep walking); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Syncope
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Pregnancy loss
PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Oropharyngeal pain; Pleural effusion; Pulmonary edema; Pulmonary fibrosis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Pain of skin; Skin and subcutaneous tissue disorders - Other (onychocryptosis); Skin and subcutaneous tissue disorders - Other (seborrheic dermatitis); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (hypovolemia)

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

7.2.14 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order agent when a patient is in screening. Expedited orders may be processed overnight Monday-Thursday when a site provides expedited courier information in OAOP.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.) All forms can be accessed on the NCI web site http://ctep.cancer.gov/forms/index.html.

***Non-Canadian International Institutions*:**
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.2.15 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:

https://ctepcore.nci.nih.gov/OAOP

- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

7.3 Clinical Trials Agreement

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

1. The Agent may not be used for any purpose outside the scope of this protocol, nor can the Agents be transferred or licensed to any party not participating in the clinical study. The Collaborator's data for the Agent are confidential and proprietary to the Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agents, each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm)
   Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to the Collaborator for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. The Collaborator will have 30 days from the date of receipt for review. The Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to the Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Email: ncicteppubs@mail.nih.gov

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

7.4 Dose Modifications (7/22/16)

Grading of toxicity will be according to Common Terminology Criteria for Adverse Events v (CTCAE) v 4. Toxicity that requires holding lapatinib should be re-evaluated at intervals of no more than 7 days. If patient meets criteria for restarting lapatinib, this may be restarted at the discretion of the investigator. If drug cannot be restarted within 14 days, the drug will be discontinued permanently. Patient, however, will stay on study. The administration of RT will not be altered for toxicities that are related to drug. Once the drug dose is reduced it will not be increased.

7.4.1 Lapatinib Dose Modification for LVEF Events

- Any patient who develops clinical signs or symptoms of cardiac failure should undergo an LVEF assessment and an ECG
- Lapatinib therapy must be discontinued permanently in case of symptomatic cardiac failure or decrease in LVEF to below the institutional normal range

7.4.2 Lapatinib Dose Modification for Non-Cardiac Events

- The maximum treatment delay for any reason is 14 days

7.4.3 Severe Cutaneous Reactions

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

INTERSTITIAL PNEUMONITIS	
Any grade	Patients who developed pulmonary infiltrates or pneumonitis must have lapatinib held while workup is ongoing. If interstitial pneumonitis is confirmed, lapatinib must be discontinued permanently.

SKIN REACTIONS	
Grade 4 rash or toxic epidermal necrolysis (eg, Stevens-Johnson Syndrome, etc.)	Permanently discontinue lapatinib

ABNORMAL LIVER FUNCTION TESTS	
Grade 2 ALT OR grade 2 bilirubin	*1st Occurrence:* Hold lapatinib until grade ≤ 1 (up to 14 days). If resumed, reduce the dose to 750 mg. *2nd Occurrence:* If toxicity recurs hold lapatinib until grade ≤ 1 (up to 14 days). If resumed, reduce the dose to 500 mg. *3rd Occurrence* If toxicity recurs again, discontinue lapatinib permanently.
Grade 2 ALT AND grade 2 bilirubin	Discontinue lapatinib permanently.
Grade 2 ALT AND INR > 1.5 if in the opinion of treating physician are both related to liver injury caused by lapatinib	Discontinue lapatinib permanently.
Grade 2 ALT OR grade 2 bilirubin with signs/symptoms that in the opinion of treating physician are related to liver injury caused by lapatinib	Discontinue lapatinib permanently (such signs and symptoms may include abdominal pain, fever, jaundice, rash, eosinophilia or a Karnofsky performance status drop of ≥ 20 points from baseline).
Grade 3 or 4 ALT and/or bilirubin	Discontinue lapatinib permanently.
DIARRHEA	
Grade 1	Continue lapatinib, but start loperamide (initial dose 4 mg followed by 2 mg every 4 hours or after every unformed stool). It is suggested to continue loperamide until the subject is free from diarrhoea for 12 hours. See Supportive care for diarrhea in Section 9.0.
Grades 2-4	*1st Occurrence:* Hold lapatinib until grade ≤ 1 (up to 14 days). Start loperamide, as above, and other measures. See supportive care for diarrhea in Section 9.0. Resume at reduced dose of 750 mg *2nd Occurrence*: Repeat above dose delay. Resume at reduced dose of 500 mg. *3rd Occurrence:* If toxicity recurs again, discontinue lapatinib permanently.

OTHER AES DUE TO LAPATINIB	
≥ Grade 3 or intolerable grade 2	*1st Occurrence:* Hold lapatinib therapy until recovery to grade ≤ 1 (up to 14 days). Resume at reduced dose of 750 mg. *2nd Occurrence:* Repeat above dose delay and resume at reduced dose of 500 mg. *3rd Occurrence:* Discontinue lapatinib permanently.

If 2 different toxicities call for different degrees of dose reduction (eg, 2nd occurrence of elevated ALT [mandating dose reduction to 500 mg/d] and 1st occurrence of diarrhea [mandating dose reduction to 750 mg/d] the lower of the 2 doses will be used (eg, 500 mg/d in the example).

See Section 9.0 for medical management of other potential events.

7.5 Modality Review

The Medical Oncology Chair, David M. Peereboom, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance with respect to drug dosing and protocol-directed dose modifications. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol, Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

This Chemotherapy Assurance Review will be performed on an ongoing basis (for example, the first review after NRG Oncology receives complete data for 20 cases and the next review after NRG Oncology receives complete data for 20 more cases). The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Oncology receives complete data for all cases, whichever occurs first.

7.6 Adverse Events (02-APR-2019)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.6.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

7.6.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.7 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.7. Contact the CTEP-AERS Help Desk if assistance is required.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

  Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.6.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis

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

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

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

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

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

7.7 CTEP-AERS Expedited Reporting Requirements (08-FEB-2018)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site,
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613
.

Submitting a report via CTEP-AERS serves as notification to RTOG and satisfies RTOG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the Additional Information section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to both the NCI at 240-276-6575 and the RTOG dedicated SAE FAX, 215-717-0990**.
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as "expedited reporting NOT required" must still be reported to fulfill RTOG safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. Important: All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

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

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements

**The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS, and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0.

- *The following are SAEs and should be reported expeditiously via CTEP-AERS:* 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 (**CTCAE, v. 4) or a ≥ 20% decrease in left ventricular cardiac ejection fraction (LVEF) relative to baseline which is below the institution's lower limit of normal.
- 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**: If bilirubin fractionation 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.
- Neurologic dysfunction should be reported as a 24h notification/5 day report. Neurologic dysfunction is defined as any grade 3 (**CTCAE v.4) signs or symptoms concerning for radionecrosis (including headache, nausea, vomiting) or neurologic deficit.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Therapy

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.

9.1.1 Dexamethasone can potentially induce CYP3A4 and therefore could theoretically decrease circulating levels of the study drug, lapatinib. On the other hand, the data supporting dexamethasone as a CYP3A4-inducing agent are not strong, and clinical need in this group of patients may be significant. Therefore, the use of dexamethasone is permitted in this study. However, because of the potential interaction, the dose should be minimized if possible. The use and dose of dexamethasone should be assessed at each study visit and documented on the case report forms.

9.1.2 Anticonvulsants

Anticonvulsant usage and dosage should be noted at the time of study entry, at each follow-up evaluation, and at any changes in medication use. Phenytoin, carbamazepine, and barbiturates are CYP3A4 inducers. If a patient requires an anticonvulsant, non-enzyme-inducing anticonvulsants are preferred (e.g., levetiracetam (Keppra) valproic acid and should be substituted if possible, under the direction of her treating physician and/or neurologist.

9.1.3 Antiemetics

Antiemetics may be used as needed. It is recommended that dexamethasone be avoided if possible.

9.1.4 Antidiarrheals

Diarrhea

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

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

9.1.5 Trastuzumab

Patients on trastuzumab at the time of study entry may continue to receive this agent throughout the study at the discretion of the treating physician. The dose and schedule will be at the discretion of the treating physician. Patients not on trastuzumab at study entry will **NOT** be permitted to begin this therapy while on protocol treatment.

9.1.6 Pertuzumab

Based on the encouraging results of the CLEOPATRA study (Baselga 2012), patients on pertuzumab at the time of study entry may continue to receive this agent throughout the study at the discretion of the treating physician. The dose and schedule will be at the discretion of the treating physician. Patients not on pertuzumab at study entry will **NOT** be permitted to begin this therapy while on protocol treatment.

9.1.7 Prior Chemotherapy (09/02/2014)

There must be at least 14 days between FINAL dose of prior chemotherapy and 1st day of protocol treatment with recovery of toxicities to grade 0 or 1.

9.2 Non-Permitted Therapy (9/7/16)

Patients not on trastuzumab, pertuzumab or any other breast cancer therapy at study entry will not be permitted to begin this therapy while on protocol treatment (ie, 6 weeks of lapatinib [SRS patients: during 6 weeks of lapatinib; WBRT patients: 3 weeks during WBRT/lapatinib + 3 weeks during post-WBRT lapatinib]). Patients may begin other drug therapy 24 hours after the completion of all protocol treatment.

Co-administration of lapatinib with strong or moderate CYP3A4/5 inhibitors (including grapefruit juice) and all CYP3A4/5 inducers is prohibited. Assess risk/benefit before co-administering lapatinib with weak CYP3A4/5 inhibitors. CYP3A4/5 inhibitors may decrease lapatinib metabolism (increasing levels); while CYP3A4/5 inducers may increase lapatinib metabolism (decreasing levels). All efforts should be made to avoid the use of therapies that induce CYP3A4 enzymes, as described in the table below

Avoid co-administration of lapatinib with drugs that are substrates of CYP3A4 or CYP2C8 and have narrow therapeutic windows.

(For Arm B DURING treatment; may be initiated immediately after treatment completion)

Drug Class	Agent	Wash-Out Prior to Protocol Treatment
CYP3A4 Inducers		
Antibiotics	All rifamycin class agents (e.g. rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	Phenytoin, carbamazepine, barbiturates (e.g. phenobarbital)	
Antiretroviral	Efavirenz, nevirapine	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	Clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	Itraconazole, ketoconazole, fluconazole (>150 mg daily), Voriconazole	
Antiretrovirals, protease inhibitors	Delavirdine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir	
Calcium channel Blockers	Verapamil, diltiazem	
Antidepressants	Nefazodone, fluvoxamine	
GI agents	Cimetidine, aprepitant	
Other	Grapefruit, grapefruit juice	
Other	Amiodarone	6 months

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the tissue/specimen submission component of this study

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission (09/02/2014)

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of tissue and whole blood banking for future research (recommended). For patients who have consented to participate in the tissue/blood component of the study. (See the sample consent).

10.2 Specimen Collection for Banking for Future Research (08-FEB-2018)

10.2.1 Tissue Submission

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

- One H&E stained slide (slide can be a duplicate cut stained H&E of the diagnostic slide (block); it does not have to be the diagnostic slide itself).
- A corresponding paraffin-embedded tissue block of the tumor (the block must match the H&E being submitted) or a 5 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. Note: A kit with the punch, tube, and instructions can be obtained free of charge from the NRG Oncology Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number and block number that corresponds to the Pathology Report and H&E slide.
- A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. 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.
- A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number.

10.2.2 Whole Blood and Plasma Submission

See Appendix II

10.2.3 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

10.2.4 Specimen Collection Summary

Specimens for Banking for Future Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary (breast) tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A corresponding paraffin-embedded tissue block of the primary (primary) tumor taken before initiation of treatment or a 5 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy (must match the H&E slide being submitted)	Block or punch shipped ambient
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-treatment, at 4 wks after WBRT/SRS completion, and at 12 wks after WBRT/SRS completion	Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Plasma sent frozen on dry ice via overnight carrier
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix	Pre-treatment. Note if site missed the collection site may collect this specimen at any timepoint or follow-up but this must be noted on the STF.	Frozen whole blood samples containing 1-1.5 ml per aliquot in 2ml cryovials (three)	Whole blood sent frozen on dry ice via overnight carrier

10.2.5 Submit materials for banking as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank- San Francisco
University of California San Francisco- box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-

Courier Address (FedEx, UPS, etc.): For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Bank- San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.3 Confidentiality/Storage (02-APR-2019)

10.3.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.3.2 Specimens for banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it upon request.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix I for a summary of time frames and assessments

11.2 Measurement of Response (7/22/16)

11.2.1 Gadolinium-enhanced brain MRI will be checked at baseline, 4 weeks after WBRT/SRS, 12 weeks after WBRT/SRS, and every 12 weeks thereafter until progression. MRI will be obtained on a 1.5T or 3Tesla scanner according to standardized imaging protocols outlined in Appendix V. MR imaging will be collected electronically for ad hoc central review of responses.

11.2.2 Response and progression in the brain is the primary endpoint of the study and will be evaluated separately from the rest of the body using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Response in the brain also will be measured using bidimensional measurements (WHO/modified McDonald's criteria). Changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

11.2.3 Response Definitions

The case report forms for this study will collect response as measured by both RECIST 1.1 and the WHO/modified McDonald Criteria separately per the definitions in the table below:

Response	RECIST 1.1 Criteria	WHO/modified McDonald Criteria
CR (complete response)	Complete disappearance of all enhancing disease and off all steroids	complete disappearance of all enhancing disease and off all steroids
PR (partial response)	**≥ 30% reduction** in the sum of diameters of up to 2 target lesions*	**≥ 50% reduction** in the sum of products of the perpendicular diameters of up to 2 target lesions* plus no new lesion, no progression of non-measurable CNS lesion, no increasing steroid requirements, and no worsening of neurologic symptoms
Stable disease	Any assessment that falls between PR and PD	Any assessment that falls between PR and PD
PD[T] (progressive disease)	• **≥ 20% increase** of up to 2 target CNS lesions relative to nadir • New CNS lesions • Unequivocal progression (defined below[‡]) • Tumor-related increase in steroid dose • New or worsening tumor-related neurologic symptoms	• **≥ 25% increase** of up to 2 target CNS lesions relative to nadir • New CNS lesions • unequivocal progression (defined below[‡]) • Tumor-related increase in steroid dose • New or worsening tumor-related neurologic symptoms

* Target lesions are defined as reliably measurable lesions and should consist of the 2 largest such lesions. Lesions with prior local treatment (e.g., SRS) are not considered measurable unless there has been demonstrated progression in the lesion (Eisenhauer 2009).

† It is encouraged that lesions previously treated with SRS be assessed with ancillary imaging (eg, PET scan).
‡ Unequivocal progression: overall level of substantial worsening in non-target lesions such that, even in presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

11.3 Central Review (7/22/16)

The study neuroradiology co-chair, Daniel Boulter, will perform a retrospective central review of the pre-study, 4-week post-WBRT/SRS, 12-week post-WBRT/SRS, and progression scans on all cases. Results from this central review will be reported, in addition to the results based on the data reported by the institutions.

11.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- A delay in protocol treatment, as specified in Section 7.0.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (08-FEB-2018)

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1720
Philadelphia, PA 19103

If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (7/22/16)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Surgical Pathology Report **(S5)** HER2 Status Documentation (pathology)	Within 2 weeks of study entry
Concurrent Treatment Form **(TF)**	1 week after concurrent treatment completion (Arm B only)
Maintenance Treatment Form **(SF)**	1 week after maintenance treatment completion (Arm B only)
Follow-up Form **(F1)**	4 weeks post-RT completion, 12 weeks post-RT completion, every 3 months to year 3, and then annually
Dosimetry Data (for Whole Brain Radiation	

Therapy Only)

- Previous SRS treatment information form (F4) — Within 1 week of study entry
- Previous SRS treatment planning (TM) (See Section 6.5 for specific details of data needed) — Within 1 week of study entry
- Radiotherapy Form (T1) — Within 1 week of RT end
- Daily Treatment Chart (T5) — Within 1 week of RT end

NOTE: ALL SIMULATION, PORTAL FILMS, IGRT AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

Scan Submission

- Pre-study MRI scan and report (MR, ME) — Within 1 week of study entry
- 4-wk post-RT MRI scan and report (MR,ME) — Within 2 weeks of scan date
- 12-wk post-RT MRI scan and report (MR,ME) — Within 2 weeks of scan date
- Progression MRI scan and report — Within 2 weeks of scan date
- Radiology review form (SR) — At 4 and 12 weeks post-RT, then every 12 weeks and at progression

12.1.1 Methods of Scan Submission

The MRI scans will be archived by Imaging and Radiation Core (IROC) using the latest version of TRIAD image submission software.

Information or questions about the MRI submission can be directed to:

Email: imagearchive@acr.org in Subject Line enter: RTOG 1119 MRI for IROC DI.
You can expect a response within 1 business day

TRIAD Digital Image Submission:

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

1. TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Philadelphia DI. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

• Site staff who submits images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account.(https://eapps-ctep.nci.nih.give/iam/index.jsp)

• To submit images, the site user must be on the site's affiliating rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

2. TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images.

TRIAD installation. Documentation can be found by following this link:

https://triadinstall.acr.org/triadclient/
Questions regarding image submissions should be directed to:
IROCPHILA-DI@acr.org.

Questions about TRIAD should be directed to:
http://triadhelp.acr.org/ClinicalTrials.aspx

Tech Support is available from Monday to Friday between 8am - 5pm EST.
Contact By Phone:
703.390.9858
Contact By Email:
Triad-Support@acr.org

12.2 Summary of Dosimetry Digital Data Submission for SRS ONLY (Submit to TRIAD; See Section 5.2) (08-FEB-2018

NOTE: ALL DIGITAL RT DATA REQUIRED IN DICOM FORMAT VIA TRIAD. ALL REQUIRED STRUCTURES MUST BE LABELED PER DICOM STANDARD NAME AS LISTED IN SECTION 6.

Preliminary Dosimetry Information (DD)	Within 1 week of RT start
Digital Data Submission – Treatment Plan submitted to TRIAD by Physicist	
Digital data submission includes the following:	
□ CT data, critical normal structures, all GTV, CTV, and PTV contours	
□ Digital beam geometry for beam sets	
□ Doses for concurrently treated beams	
□ Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan □ All required structures **MUST** be labeled per the table in Section 6 Submit via TRIAD with the digital data listed above.	
Upon submission of the digital data via TRIAD, complete an online digital data transmission form (DDSI) located in the CORE LAB section on the NRG Oncology/RTOG web site at https: www.irocqa.org/Resources/TRIAD-for-RT-QA	
Note: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.	

Final Dosimetry Information	Within I week of RT end
Radiotherapy Form (T1)	
Daily Treatment Record (T5)	

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints (7/22/16)

13.1.1 Primary Endpoint

Complete response (CR) rate in the measurable brain metastases at 12-weeks post whole brain irradiation (WBRT) or stereotactic radiosurgery (SRS) (measured using revise RECIST version 1.1 based on MRI scan of the brain – see Section 13.4 for details)

13.1.2 Secondary Endpoints

- Complete response (CR) rate of measurable brain metastases at 4 weeks post WBRT/SRS
- Objective response rate (CR + PR) of measurable brain metastases at 4 and 12 weeks post WBRT/SRS
- Targeted lesion-specific objective response rate (CR + PR) at 4 and 12 weeks post WBRT/SRS
- CNS progressive disease out the targeted measurable disease
- Targeted lesion-specific progression at 4 and 12 weeks post WBRT/SRS
- Treatment-related adverse events as measured by CTCAE v 4
- Overall CNS complete response as defined in Section 2.2.7
- Over CNS progressive disease (within or outside measurable disease)
- Overall survival (OS) (failure: death due to any cause)

13.2 Stratification (7/22/16)

Patients will be stratified before randomization with respect to graded prognostic assessment (GPA) score (1.5-2 vs 2.5-3 vs 3.5-4); use of non-CNS–penetrating HER2 blockade at time of study entry (No vs. Yes: trastuzumab ± pertuzumab); and RT to be used (WBRT vs. SRS). The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution.

13.3 Sample Size and Power Justification (7/22/16)

13.3.1 The study will be a randomized phase II screening trial as proposed by Rubinstein et al (2005). Specifically, this randomized phase II trial will evaluate if there is a sufficient enough signal in improved 12-week (post WBRT/SRS) CR rate with the addition of lapatinib to WBRT/SRS in patients with brain metastasis from HER-2 positive breast cancer to warrant a future phase III trial. The null hypothesis is that the 12-week post WBRT/SRS CR rate is ≤ 5% for both WBRT/SRS (control arm, Suh, ENRICH study, personal communication) and WBRT/SRS + lapatinib (experimental arm). The alternative hypothesis is that the addition of lapatinib to WBRT/SRS will result in a 12-week post WBRT/SRS CR rate of at least 20%. The randomization of experimental and control arms is set as 1:1. With 114 eligible subjects there will be 86% power to detect a 15% absolute increase in CR rate at a significance level of 0.10, using a 1-sided *Z*-test for 2 proportions. Guarding against up to 5% of ineligibility rate and 15% patients not evaluable for the primary endpoint due to death, patient withdrawal, or other reasons, the final targeted accrual for this study component will be 143 cases. In the event that the WBRT/SRS CR rate is ≤ 10% for WBRT/SRS (control arm), 114 eligible patients provides 80% power to detect a 15% absolute increase to at least 25% in CR rate with the addition of lapatinib at a significance level of 0.10, using a 1-sided *Z*-test for 2 proportions.

No Sample Size Change with SRS Amendment

The amendment to allow RT delivery with SRS will not change the planned sample size, as described below. The current sample size provides 86% statistical power to detect an increase in the 12-week CR rate from 0.05 to 0.20. The current statistical section of the protocol also already states that in the event that the control arm rate is up to 0.10, the sample size provides 80% power to detect the hypothesized 15% absolute increase.

Under the assumption that patients treated with SRS have a 12-week CR rate of 0.14, the overall control arm 12-week CR rate will be higher than 0.05, but how much higher will depend on the proportion of SRS treated patients entered onto the trial. As the

planned accrual is already halfway completed and assuming a 0.14 CR rate for patients treated with SRS, the table below shows what the overall control arm rates would be for the proportion of patients receiving SRS ranging from 10-50%.

% of WBRT Patients (Assuming 12 wk CR rate of 0.05)	% of SRS Patients (Assuming 12 wk CR rate of 0.14)	Overall CR rate for control arm
100% - original design	0%	0.05
90%	10%	0.059
80%	20%	0.068
70%	30%	0.077
60%	40%	0.086
50%	50%	0.095

As shown in the table above, even if all of the rest of the patients receive RT via SRS, the control arm 12-week CR rate would not exceed 0.10, and therefore the original planned sample size provides sufficient power to address the primary hypothesis.

13.3.2 Patient Accrual (09/02/2014)

Patient accrual is projected to be 6 cases per month. With a 6-month ramp-up period with little to no accrual while the study is approved by institutional IRBs, accrual is projected to be completed in 30 months. The study will officially be reviewed for accrual by the NRG Oncology Data Monitoring Committee at the NRG Oncology semi-annual meetings. Eighteen months post activation, if the average monthly accrual rate in months 13 to 18 is less than 3 patients, the study will be re-evaluated with respect to feasibility. If this occurs, considerations will be given to revising the eligibility to increase accrual.

13.4 Analysis Plan (7/22/16)

All analyses will be done based on the assigned treatment arm for all eligible patients entered.

13.4.1 Statistical Methods

Complete Response (CR) Rate

Response in the brain is the primary endpoint of the study and will be evaluated separately from the rest of the body using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Response in the brain also will be measured using bidimensional measurements (WHO/modified McDonald's criteria). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Non-CNS lesions are considered non-target lesions. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

For patients who received prior SRS, response will be based on the new (protocol-treated) lesion(s).

For a given treatment arm, the CR rate will be calculated by dividing the number of patients classified as CR by the number of analyzable patients. A Z-test will be used to compare the CR rates between the treatment arms.

Response Definitions

- Objective response (CR + PR) will be based on up to 2 target lesions and will evaluated based on responses reported by the institution and also evaluated based on a central review of MRIs.
- Lesion-specific response will be performed for up to 2 target lesions based on responses reported by the institution and also evaluated based on a central review of MRIs. Lesion-specific response for up to 8 additional non-target lesions will based on a central review of MRIs.

Overall response will be defined per the following table:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = inevaluable PD = progressive disease; PR = partial response; SD = stable disease.

Overall Survival (OS)

OS will be estimated by the Kaplan-Meier method (Kaplan 1958). The distribution of OS estimates between the two arms will be compared using the log rank test (Mantel 1966). OS time will be measured from the date of randomization to the date of first failure or last follow-up. The Cox proportional hazard regression model will be used to analyze the effects of factors, in addition to treatment, that may be associated with OS (Cox 1972).

13.4.2 Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing),
- total patients accrued,
- distributions of important pretreatment and prognostic baseline variables,
- the frequencies and severity of adverse events by treatment arm, and
- compliance rates of treatment delivery.

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, 12-week post WBRT/SRS CR rate, or any secondary endpoints, with the exception of reporting of adverse events.

13.4.3 Data and Safety Monitoring

This study will be reviewed by the RTOG Data Monitoring Committee (DMC) on a semiannual basis for accrual (while applicable) and adverse events.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.4 Analysis for Reporting the Initial Treatment Results

The primary hypothesis of this study is that the addition of lapatinib to WBRT/SRS will increase the 12-week post WBRT/SRS CR rate from 10% to 25%, for patients with brain metastasis from HER-2+ breast cancer. This analysis will occur after the last patient has been followed for a minimum of 12 weeks after WBRT/SRS. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given,
- distributions of important prognostic baseline variables,
- the frequencies and severity of adverse events by treatment arm,
- compliance rate of treatment delivery, and
- observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using the Z-test comparing 1 proportions with a significance level of 0.10. Additional analyses of treatment effect will be performed using the logistic regression model with the stratification factor included as a fixed covariate, as well as any factors that show an imbalance between the arms.

13.5 Gender and Minorities

Both men and women of all races and ethnic groups are eligible for this study. In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, possible interaction between race/ethnicity and treatment have been considered. A statistical analysis will be performed to examine the possible difference between among the races, as accrual across classes of race permits. Based on previous RTOG studies, it is projected that: 4% will be of Hispanic or Latino ethnicity and 96% will not; racial distribution will be 58% white, 30% Asian, 11% black or African American, and 1% American Indian or Alaskan Native: The following table lists the projected accrual by ethnic and racial categories.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	6	0	6
Not Hispanic or Latino	137	0	137
Ethnic Category: Total of all subjects	143	0	143
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	2	0	2
Asian	43	0	43
Black or African American	15	0	15
Native Hawaiian or other Pacific Islander	0	0	0
White	83	0	83

	Gender		
Ethnic Category	Females	Males	Total
Racial Category: Total of all subjects	143	0	143

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APPENDIX I (7/22/16)

STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

Assessments	**Time Point**		
	Prior to registration	≤ 21 days prior to registration	≤ 7 days prior to treatment start
Histo/cyto eval	X		
T1-weighted gadolinium-enhanced MRI of brain		X	
History/physical		X	
Performance status		X	
ANC, platelets, Hgb		X	
Creatinine, AST		X	
Bilirubin		X	
ALT		X	
Serum pregnancy test (if applicable)		X	
Serum or urine pregnancy test (if applicable)			See Section 4.1
Tissue for banking (for consenting pts)	Prior to start of treatment		
Plasma for banking (for consenting pts)	Prior to start of treatment		
Whole blood for banking (for consenting pts)	Prior to start of treatment (if site misses pretreatment time point, collection may occur at any other time point or follow-up visit)		

APPENDIX I (cont'd)

STUDY PARAMETER TABLE: DURING TREATMENT ASSESSMENTS

Assessments	**Time Point**		
	After 7 days of WBRT (for SRS patients: 7 days after SRS)	After 14 days of WBRT (for SRS patients: 14 days after SRS)	At end of WBRT
Bilirubin			Arm B only; repeat wkly if 1st sample triggers dose modification or hold; otherwise repeat not needed
ALT			Arm B only repeat wkly if 1st sample triggers dose modification or hold; otherwise repeat not needed
Adverse Event eval	X	X	X

STUDY PARAMETER TABLE: FOLLOW-UP ASSESSMENTS

Assessments	**Time Point**		
	28 days after WBRT/SRS completion	12 weeks after WBRT/SRS completion	Then every 12 weeks
T1-weighted gadolinium-enhanced MRI of brain	X	X	X (until progression)
Performance status	X	X	X
Adverse event eval.	X	X	
Plasma for banking (for consenting pts)	X	X	

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	**Normal; no complaints; no evidence of disease**
90	**Able to carry on normal activity; minor signs or symptoms of disease**
80	**Normal activity with effort; some sign or symptoms of disease**
70	**Cares for self; unable to carry on normal activity or do active work**
60	**Requires occasional assistance, but is able to care for most personal needs**
50	**Requires considerable assistance and frequent medical care**
40	**Disabled; requires special care and assistance**
30	**Severely disabled; hospitalization is indicated, although death not imminent**
20	**Very sick; hospitalization necessary; active support treatment is necessary**
10	**Moribund; fatal processes progressing rapidly**
0	**Dead**

APPENDIX III (08-FEB-2018)
NRG Oncology FFPE Specimen Plug Kit Collection
NRG Oncology Blood Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For Formalin fixed paraffin embedded (FFPE) or Non-frozen Specimens Only

NRG Oncology Biospecimen Resource
University of California San Francisco
Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-

Courier Address (FedEx, UPS, etc.): For ALL Frozen or Trackable Specimens
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (ST) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

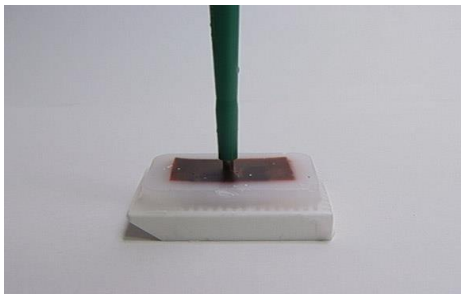
- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it might I break during shipping.
  - ○ Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep Serum, Plasma, and Whole Blood specimens in separate bags.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

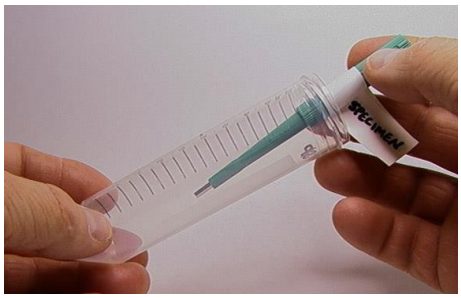
- ❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bankby e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

NRG ONCOLOGY FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

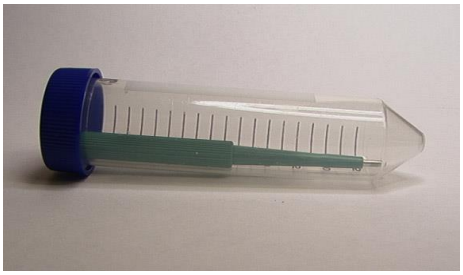


Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.



Step 2
Label the punch tool with the proper specimen ID and block ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bankand we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: RTOGNRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: <u>For Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank- San Francisco
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For ALL Frozen Specimens or Trackable shipments</u>
NRG Oncology Biospecimen Bank- San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of <u>plasma or whole blood</u> *(as specified by the protocol)*:

<u>Kit contents</u>:Sites are responsible for providing their blood draw tubes

- Fifteen (15) 1 ml cryovials for plasma
- Three (3) 2ml cyrovials for whole blood
- Biohazard bags (4) and Absorbent shipping material (4
- One Styrofoam container (inner) and Cardboard shipping (outer) box per case
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

<u>PREPARATION AND PROCESSING OF PLASMA AND WHOLE BLOOD:</u>

(A) <u>Plasma (If requested): Purple Top EDTA tube #1</u>

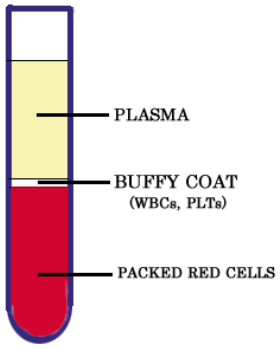
- ❑ Label five1ml cryovials (as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials “plasma”.

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STForm.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot a minimum of 0.5 ml plasma into fivecryovials as are necessary for the plasma collected () labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

(continued on next page)



(B) <u>Whole Blood for DNA (if requested): Purple Top EDTA tube #2</u>

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0-1.5 ml blood into three cryovials as are necessary for the blood collected labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze tubes upright immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STForm.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

<u>Shipping/Mailing</u>:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.

- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOGNRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: RTOGNRGBB@ucsf.edu

APPENDIX IV

GRADED PROGNOSTIC ASSESSMENT FOR BREAST CANCER (BREAST-GPA)

Prognostic Factor	**0**	**0.5**	**1.0**	**1.5**	**2.0**		**Score**
Karnofsky Performance Status	≤ 50	60	70-80	90-100	n/a		____
Subtype	Basal	n/a	LumA	HER2	LumB		____
Age	≥ 60	< 60	n/a	n/a	n/a		____
						Sum Total	____
Subtype:	Basal =	Triple Negative (ER/PR/HER2-neg)					
	LumA =	Luminal A (ER/PR-pos, HER2-neg)					
	LumB =	Luminal B (Triple Positive, ER/PR/HER2-pos)					
	HER2 =	HER2-pos, ER/PR-neg					

MST (mo) by GPA: 0-1.0 = 3.4, 1.5-2.0 = 7.7, 2.5-3.0 = 15.1, 3.5-4.0 = 25.3

Sperduto PW, Kased N, Roberge D, et al. Effect of tumor subtype on survival and the Graded Prognostic Assessment (GPA) for patients with breast cancer and brain metastases. *Int J Radiat Oncol Biol Phys*. 2011;Apr14 (Epub ahead of print).

Sperduto PW, Kased N, Roberge D, et al. Summary report on the Graded Prognostic Assessment (GPA): an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastasis. *J Clin Oncol.* 2012;30:419-25.

Appendix V (7/22/16)

Consensus Recommendations for a Standardized Brain Tumor Imaging Protocol in Clinical Trials

Minimum standard 1.5 T & 3 T MRI protocol[l]

	3D T1w Pre[b]	Ax 2D FLAIR[j]	Ax 2D DWI	Ax 2D T2w[h,i] (Contrast Injection[a)]	3D T1w Post[b] (Contrast Injection[a)]
Sequence	IR-GRE[e,f]	TSE[c]	SS-EPI[g]	TSE[c]	IR-GRE[e,f]
Plane	Sagittal/axial	Axial	Axial	Axial	Sagittal/axial
Mode	3D	2D	2D	2D	3D
TR [ms]	2100[m]	>6000	>5000	>2500	2100[m]
TE [ms]	Min	100–140	Min	80–120	Min
TI [ms]	1100[n]	2000–2500[k]			1100[n]
Flip angle	10°–15°	90°/≥160°	90°/180°	90°/≥160°	10°–15°
Frequency	≥172	≥256	≥128	≥256	≥172
Phase	≥172	≥256	≥128	≥256	≥172
NEX	≥1	≥1	≥1	≥1	≥1
FOV	256 mm	240 mm	240 mm	240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm[l]	≤4 mm[l]	≤4 mm[l]	≤1.5 mm
Gap/spacing	0	0	0	0	0
Diffusion options[p]			*b* = 0, 500, 1000 s/mm^2 ≥3 directions		
Parallel imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x
Scan time (approx) [benchmarked on 3 T Skyra]	5–10 min [5:49 for 1 mm isotropic]	4–8 min [3:22 for 2D FLAIR]	2–4 min [1:22 for 3 direction DWI and 3 b-values]	4–8 min [5:10 for dual echo]	5–10 min [5:49 for 1 mm isotropic]

Abbreviations: 2DFL, 2-dimensional FLASH (fast low angle shot) gradient recalled echo; 3D, 2-dimensional; A/P, anterior to posterior; ADC, apparent diffusion coefficient; Ax, Axial; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; EPI, echo-planar imaging; FLAIR, fluid-

attenuated inversion recovery; FOV, field of view; GE-EPI, gradient-echo echo-planar imaging; IR-GRE, inversion-recovery gradient-recalled echo. MPRAGE, magnetization prepared rapid gradient-echo; NEX, number of excitations or averages; PD, proton density; R/L, right to left; SS-EPI, single-shot echo-planar imaging; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin-echo.

[a]0.1 mmol/kg dose injection with a gadolinium-chelated contrast agent. Use of a power injector is desirable at an injection rate of 3–5 cc/s.

[b]Postcontrast 3D T1-weighted images should be collected with equivalent parameters to precontrast 3D T1-weighted images.

[c]TSE = turbo spin-echo (Siemens & Philips) is equivalent to FSE (fast spin-echo; GE, Hitachi, Toshiba).

[d]FL2D = 2-dimensional fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1-fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.

[e]IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[f]A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[g]In the event of significant patient motion, a radial acquisition scheme may be used (eg, BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerably more time.

[h]Dual echo PD/T2 TSE is optional for possible quantification of tissue T2. For this sequence, the PD echo is recommended to have a TE < 25 ms.

[i]Advanced sequences can be substituted into this time slot, so long as 3D postcontrast T1-weighted images are collected between 4 and 8 minutes after contrast injection.

[j]3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE = 90–140 ms; TR = 6000–10 000 ms; TI = 2000–2500 ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA ≤ 2; fat saturation; slice thickness ≤1.5 mm; orientation sagittal or axial; FOV ≤ 250 mm × 250 mm; matrix ≥244 × 244.

[k]Choice of TI should be chosen based on the magnetic field strength of the system (eg, TI ≈ 2000 milliseconds for 1.5 T and TI ≈ 2500 milliseconds for 3 T).

[l]In order to ensure comparable SNR, older 1.5 T MR systems can use contiguous (no interslice gap) images with 5 mm slice thickness or increase NEX for slice thickness ≤4 mm.

[n]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400–450 milliseconds for similar contrast.

[m]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5–15 milliseconds for similar contrast.

[p]Older model MR scanners that are not capable of >2 *b* values should use *b* = 0 and 1000 s/mm^2.

1. Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. *Neuro-oncology* 2015; 17(9): 1188-98.