RADIATION THERAPY ONCOLOGY GROUP

RTOG 0320

A PHASE III TRIAL COMPARING WHOLE BRAIN RADIATION AND STEREOTACTIC RADIOSURGERY ALONE VERSUS WITH TEMOZOLOMIDE OR GEFITINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND 1-3 BRAIN METASTASES

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INDEX

Schema

Eligibility Checklist

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Recommended Pretreatment Evaluations

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Tissue/Specimen Submission

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix III - Neurologic Function (NF) Status
Appendix IV - Study Agent Shipment Form
Appendix V - Stereotactic Radiotherapy QA Guidelines
Appendix VI - Stereotactic Facility Questionnaire
Appendix VII - Drugs that Interfere with Iressa Metabolism
Appendix VIII - Enzyme vs. Non-enzyme Inducing Anti-Seizure Medications

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SCHEMA

STRATIFY

***RPA Class**
1. Class I: < 65 years *and* no extra-cranial metastases
2. Class II: ≥ 65 years *or* extra-cranial metastases

Number of Metastases
1. One
2. Two or three

Extent of Extracranial Disease
1. None
2. Present

RANDOMIZE

Arm 1: WBRT + SRS

Arm 2: WBRT + SRS + temozolomide

Arm 3: WBRT + SRS + Gefitinib

*****See Section 13.4.2

Arm 1: WBRT (2.5Gy x 15 to 37.5Gy) and SRS to all 1- 3 metastases within two weeks after completion of WBRT.

Arm 2: WBRT + SRS + temozolomide 75mg/m^2/day for 21 days, beginning on day 1 of WBRT; then four weeks after the completion of WBRT, 150mg/m^2/day for 5 days/month if prior or concurrent chemotherapy (200mg/m^2/day for 5 days/month if no prior chemotherapy) until progression (systemic or brain) or for a maximum of 6 additional cycles.

Arm 3: WBRT + SRS + Gefitinib 250mg/day daily beginning on day one of WBRT and continuing up to progression (brain) or a maximum of 6 months after completion of WBRT + SRS

See Section 7.0 for chemotherapy details.

Patient Population (See Sections 3.0 for Eligibility and 5.0 for Pre-Registration Requirements.)

- Histologically confirmed non-small cell lung cancer with 1-3 intraparenchymal brain metastases
- Well-circumscribed intraparenchymal brain lesion with maximum tumor diameter (≤4.0 cm per lesion). If multiple lesions are present and one lesion is at the maximum diameter, the other*(s)* must not exceed 3.0 cm in maximum diameter.
- Patients who have undergone **sub**total resection are eligible providing residual disease is ≤4.0 cm in maximum diameter.
- No metastases to brain stem, midbrain, pons, medulla or within 10 mm of the optic apparatus *(optic nerves and chiasm)*.
- No clinical or radiographic evidence of progression of extracranial disease in the month prior to randomization. (Patients who present with symptoms of brain metastases at the time of initial diagnosis are eligible and do not need to demonstrate one month of stable scans.)

Required Sample Size: 381

RTOG Institution # _____

RTOG 0320 **ELIGIBILITY CHECKLIST (10/06/04)**

Case # _____ (page 1 of 2)

_____(Y) 1. Is there histologic proof of non-small cell lung cancer?

_____(Y) 2. Has a contrast enhanced, diagnostic brain MRI been done within 2 weeks prior to registration?

_____(Y) 3. Does the imaging demonstrate the presence of one to three intraparenchymal brain metastases?

_____(Y) 4. Is the maximum tumor diameter ≤4.0 cm?

_____(N) 5. If multiple lesions are present and one is at the maximum diameter, do any of the others exceed 3.0 cm in diameter?

_____(Y/N) 6. Has patient undergone **sub**total resection?
_____(Y) If yes, does residual disease measure ≤ 4.0 cm in maximum diameter?

_____(N) 7. Has the patient had any previous cranial radiation?

_____(N) 8. Will the patient have received treatment with a non-approved or investigational systemic agent with 30 days prior to the start of study treatment?

_____(Y) 9. Is the patient 18 years or older?

_____(Y) 10. Is the Zubrod Performance Status 0-1?

_____(0-2) 11. Is the Neurologic Function Status 0, 1, or 2 (per Appendix III)?

_____(Y) 12. Have required prestudy evaluations been obtained and do the laboratory values meet the criteria in Sections 3.1.9 and 3.1.10?

_____(N) 13. Has the patient had any clinical or radiographic evidence of progression other than the study lesion in the last month? (Patients who are found to have one to three brain metastases at the time of initial diagnosis are eligible and do not need to demonstrate one month of stable scans if they meet the other eligibility criteria.)

_____(N) 14. Any evidence of leptomeningeal metastases?

_____(N) 15. Are there any metastases to the brain stem, midbrain, pons, or medulla, within 10 mm of the optic apparatus?

_____(N) 16. Is there evidence of liver metastases?

_____(N) 17. Is patient pregnant or nursing?

_____(N) 18. Is patient known to be HIV positive?

_____(N) 19. Any evidence of clinically active interstitial lung disease?

_____(N) 20. Will patient be treated with concomitant St. John's Wort?

_____(Y) 21. Has the patient signed a study-specific consent form?

RTOG Institution # _____

RTOG 0320 **ELIGIBILITY CHECKLIST (10/06/04)**
Case # _____ (page 2 of 2)

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

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

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

_____ 5. Patient's Initials (First Middle Last) [May 2003. If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

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

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Treatment Start Date

_____ 17. Medical Oncologist

_____ 18. RPA Class (Class I vs. Class II) (If "Class I," then # 20 must be "none.")

_____ 19. Number of Metastases (one vs. two or three)

_____ 20. Extent of Extracranial Disease (none vs. present)

_____ 21. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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/RTOG audit.

Completed by _____ Date _____

1.0 BACKGROUND

1.1 Hypothesis

For patients with non-small cell lung cancer and 1-3 brain metastases, whole brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) plus either temozolomide or gefitinib will result in better survival than WBRT + SRS alone.

1.2 Epidemiology

Metastases to the brain are the most common malignancy affecting the brain.[1,2,3] Autopsy series have shown that as many as 25% of patients who die of cancer will have intracranial metastases, involving brain parenchyma in about 15%.[3,4] The majority of patients with intraparenchymal metastases have only one or two or three metastases, 49%, 21%, and 10%, respectively, and the remaining 20% have more than three. Approximately 80% of brain metastases are located supratentorially.[5]

Historically, the standard treatment for patients with brain metastases has been glucocorticoids and whole brain irradiation *(WBRT)* which effectively relieve symptoms and restore neurological function in most patients.[6] Untreated patients have a median survival time *(MST)* of less than 7 weeks.[7] Three prospective randomized trials involving more than 1800 patients conducted by the Radiation Therapy Oncology Group *(RTOG)* evaluated 9 different radiation doses and schedules.[8] All doses up to 50 Gray *(Gy)* were equivalent with respect to toxicity, neurological improvement, and survival. Higher doses resulted in greater neurologic toxicity. Median survival time (MST) of all patient subgroups was three to six months. Little difference was found between patients who received 20 Gy administered over one week and 40 Gy administered over four weeks. Furthermore, radiation boost treatment to the metastatic site did not improve these parameters when compared to WBRT.[9] Detailed quality of life measurement tools were not part of these studies.

The most common cancers to metastasize to brain are lung and breast, 34% and 30%, respectively. Of the approximately 200,000 patients with these malignancies who will die each year, 124,000 will have brain metastases.[10] The cause of death in almost 30-50% is persistence of lesions or recurrence following WBRT; however, 10% to 15% of patients will survive at least one year.[11,12] These data, along with the fact that brain metastases are so frequently three or fewer, provide the rationale for the development of treatment modalities that exceed current palliative measures to actually improve patient survival, neurocognitive function and/or quality-of-life.

1.3 Surgery Literature Review

There is extensive literature on the surgical management of brain metastases. The salient literature can be briefly summarized as follows. Surgical resection of solitary brain metastases is increasingly performed on patients with favorable prognostic factors, accessible lesion*(s)*, and/or metastatic lesions from relatively radio-insensitive tumors such as renal cell carcinoma and melanoma.[3,13,14,15,16,17,18] Since metastases are usually well demarcated from surrounding brain, complete removal with a minimum of morbidity and mortality is often possible. Relief of symptoms of intracranial hypertension and focal brain dysfunction has been demonstrated. Patient survival is also dependent on the extent of extracranial disease. Resection preceding WBRT appears to improve survival compared to WBRT alone.[19] Two prospective randomized trials in which surgical excision followed by radiation therapy compared to radiation therapy alone in patients with single metastases have been done. Patchell and colleagues randomized patients with single metastases to either surgical excision followed by WBRT (25 pts) or biopsy followed by WBRT (23 pts).[20] The MST of patients who underwent surgical resection rather than biopsy were 40 and 21 weeks, respectively; functional independent survival times were 38 and 8 weeks, respectively, and the intracranial recurrence rates 20% and 52%, respectively. These results confirmed those of an earlier uncontrolled study showing the benefits of surgical resection.[15] Vecht et al. randomized 63 patients to the same regimens with similar results.[21,22] Bindal et al., in a retrospective analysis of 56 patients with multiple resected metastases, 50% of whom received WBRT, reported a MST equivalent to that of patients with a single resected metastasis but longer than that of patients who had one or more lesions remaining after surgery.[22] Based on these reports, surgical removal in patients with a solitary accessible lesion followed by WBRT appears superior to WBRT alone for selected patients.

The post-operative delivery of WBRT for such patients has been considered beneficial to sterilize residual disease in the tumor bed or other sites of occult disease in the brain. For patients who have undergone removal of solitary brain metastases, the addition of WBRT appears to result in a lower incidence of brain recurrence. The University of Kentucky randomized patients with single brain metastases to surgery alone (46 patients), or surgery followed by WBRT (49 patients).[23] Although MST and functional independence survival times of the two groups were similar, local recurrence occurred in 46% and 10%, respectively with distant recurrence 37% and 14%. Death due to neurologic disease was 44% and 14%.

There are several retrospective studies involving relatively small numbers of patients in which surgery followed by WBRT has been compared to surgery alone.[16,24,25,26] Smalley and colleagues demonstrated a statistically significant benefit in survival and fewer recurrences in 85 patients who received WBRT following surgery.[24] In a second retrospective analysis by the same investigators, the MST among 229 patients was 15 months for those who underwent surgery followed by adjuvant WBRT as compared to 8 months for patients who underwent surgery but did not receive WBRT.[25] On the other hand, Hagan et al. found no advantage to WBRT following surgery in patients with melanoma, a radioresistant tumor.[16] Likewise, Dorsoretz et al. found no survival advantage to low dose WBRT among 33 patients with resected solitary lesions and no active systemic cancer.[26]

1.4 Radiosurgery Literature Review

There is extensive literature suggesting stereotactic radiosurgery is as good or better than surgical resection in terms of local control and is noninvasive and more cost-effective.[27,28,29] Over a decade of reports have suggested a role for stereotactic radiosurgery *(SRS)* in the treatment of metastatic brain tumors.[13,30-43] The development of linear accelerators modified to deliver focused irradiation has expanded the availability of SRS.[44,45,46] Advantages of SRS are ease of administration from the patient's viewpoint *(a one-day noninvasive treatment usually performed as an outpatient)*, the ability to treat metastases located in areas of the brain not amenable to complete surgical resection, and the potential to decrease neurosurgery and radiation related morbidity and mortality.[46-49] SRS allows delivery of a high dose of focal irradiation in a single fraction to the tumor from multiple angles.[50] Brain metastases are ideal targets for SRS because the majority are small *(< 3 cm in diameter)*, most are spherical with distinct tumor margins on contrast enhanced imaging studies and most displace rather than infiltrate normal brain.[44] SRS minimizes the amount of radiation received by the non-target regions of the brain, and the area targeted generally does not include functional brain.[36,46]

Retrospective analyses show that brain metastases from a large number of different types of malignancies including less radioresponsive malignancies such as colon cancer, renal cell carcinoma and melanoma respond to SRS.[39,42,51,52] Local control to complete radiographic obliteration has been achieved in 80% to 90% of cases.[46,51,53,54] Noordijk et al. treated 52 brain metastases in 33 patients with SRS.[55] At 5.5 months follow up, 10 *(29%)* patients' metastatic lesions had completely disappeared, 15 *(50%)* had decreased in size and four had stable intracranial disease. Mehta et al. reported the results of a prospective trial in which patients with single brain metastasis were randomized to undergo surgical resection of the metastasis followed by SRS to the preoperative tumor margins and/or residual tumor or SRS alone[43]. MST for patients who received surgery and SRS was 40 weeks compared to 15 weeks for patients who received SRS alone. There were fewer recurrences at the site of the original brain metastasis in patients who underwent surgery plus SRS compared to SRS alone, 20% vs 52%, respectively. The quality of life of patients in the former group was also markedly improved. Variable affecting response and complications include performance status, patient age and lesion size.[32,37,48,56,57]

1.4.1 RTOG Radiosurgery Experience

The RTOG has been at the forefront of clinical trials on the management of patients with brain metastases since the 1970s. In addition to the trials in the pre-radiosurgery era described in Section 1.2, there is now a significant database in the radiosurgery era.

The RTOG dose-escalation study (RTOG 9005) reported the maximum tolerated radiosurgery dose in patients with recurrent irradiated primary brain tumors and brain metastases (n=156) for lesions of $\leq$ 2.0cm, 2.1-3.0cm and 3.1-4.0cm in maximum diameter were 24Gy, 18Gy and 15Gy, respectively.[58]

Sanghavi et al[59] recently reported a retrospective multi-institutional recursive partitioning analysis (RPA) suggesting there was a significant survival benefit for patients treated with WBRT plus SRS when compared to an RTOG database of patients treated with WBRT alone and that this benefit existed in all three RPA classes.

Sperduto et al recently reported a prospective randomized RTOG trial (RTOG 9508) of WBRT versus WBRT plus SRS for patients with 1-3 brain metastases.[60] WBRT plus SRS provided a survival advantage compared to WBRT alone in each of the following patient categories: 1) solitary brain metastases (for which the study was stratified) and the following subsets; 2) 1-3 metastases and RPA class I; 3) 1-3 metastases and age < 50 years and; 4) 1-3 metastases and non-small cell lung cancer or any squamous carcinomas. Furthermore, all subsets of patients in the WBRT + SRS group were more likely to have a stable or improved performance status, improved local control and reduced steroid dependence compared to the WBRT alone group. Systemic disease remained the primary cause of death (> 2/3) in both groups. Adverse events and the rate of re-operation were comparable in the two groups. Re-operation pathology showed necrosis in all patients in the WBRT + SRS arm and viable tumor in all patients in the WBRT alone arm.

1.5 WBRT: Pro and Con

Despite the wealth of literature referenced above, there remain conflicting data, and opposing practice patterns are emerging regarding whether WBRT is beneficial or not when added to SRS. Several prominent institutions are treating selected patients with SRS alone.

Pro: As previously discussed, in the Patchell et al trial in which patients were randomized with single brain metastasis to surgery alone vs. surgery followed by WBRT, the patients in the WBRT group were less likely to die of neurologic causes than patients in the observation group (14% vs. 44%, $p = 0.003$).[20] This is despite the fact that among the 70% of patients in the observation group who experienced a brain tumor recurrence, 88% received salvage WBRT either alone or in combination with surgery or SRS. More recent reports from the University of Kentucky show that despite the use of high resolution treatment planning and close follow-up MRI in patients with newly diagnosed brain metastases, use of SRS alone is associated with an increasing risk of brain recurrence with increasing survival time.[61,62] In addition, the majority of such recurrences are symptomatic and associated with a neurologic deficit.

Con: A recent report from UCSF by Sneed and associates [63] suggested that radiosurgery alone results in equivalent survival and intracranial control when compared to radiosurgery and WBRT for one to four metastases to brain. In this retrospective report 62 patients treated with radiosurgery alone were compared to 43 treated with both modalities. Survival was 11.3 and 11.1 months, respectively. Remote failure was higher in the radiosurgery group (72% vs. 31%), but high successful salvage resulted in intracranial control 62% and 73% (not significantly different), respectively. It should be noted that selection bias was acknowledged and evident as there was a statistically significant greater number of patients with solitary metastases in the SRS alone arm.

Based on the results of RTOG 9508, and with full consideration of the above WBRT debate, this trial will consider WBRT plus SRS the standard treatment arm. The two experimental arms and their rationale are described in Sections 1.6 and 1.7.

1.6 Temozolomide

There are extensive data supporting the use of temozolomide and radiation as proposed. These include at least 3 different clinical settings, including over 300 patients with NSCLC with brain metastases treated with the agent and reported in several clinical trials. In addition, in a fourth setting, i.e. NSCLC without brain metastases, temozolomide demonstrates activity comparable to the FDA approved agent Taxotere, in the second line context. These clinical trials include:

1.6.1 Clinical Setting 1: Trials in which temozolomide is used as a salvage agent post-radiotherapy. In general, these trials have included patients with multiple histologies, and overall response rates have been low; for non-small cell lung cancer brain metastases in particular, these have ranged from 0-20% response rates. The key studies using temozolomide in this recurrent context are summarized below:

Christodolou, et al: Ann Oncol, 12:249-254, 2001; overall response rate with temozolomide was 4% in 17 NSCLC patients with recurrent/progressive brain metastases.[64]
Abrey, et al: J Neuro Oncol, 53:259-265, 2001; overall response rate with temozolomide was 9% in 22 NSCLC patients with recurrent/progressive brain metastases.[65]
Friedman, et al: ASCO Proc, 2003 abstract # 408; overall response rate with temozolomide was 7% in 29 NSCLC patients with recurrent/progressive brain metastases.[66]
Giannitto-Giorgio C et al: Ann Oncol 13:148, abstract 541, 2002 and Proc Am Soc Clin Oncol. 2002; 21: Abstract 2779; overall response rate with temozolomide was 20% (and an additional 6 patients had stable disease) in 15 NSCLC patients with recurrent/progressive brain metastases.67 (Preliminary results of these data have been presented at ESMO, 2002. Additionally, this same group will be reporting (at the next Italian Meeting of Oncology) observed temozolomide responses in NSCLC patients with progressive CNS disease.

One small study by Dziadziusko et al. involving 12 NSCLC patients with brain mets and 13 without brain mets did not demonstrate activity in either group of patients. (Dziadziuszko R, Ardizzoni A, Postmus PE, Smit EF, Price A, Debruyne C, Legrand C, Giaccone G; EORTC Lung Cancer Group. Temozolomide in patients with advanced non-small cell lung cancer with and without brain metastases. a phase II study of the EORTC Lung Cancer Group (08965). *Eur J Cancer*. 2003 Jun;39(9):1271-6.)
There is one other trial where this population has been studied with similar results (Mangiameli).[68]
In summary, in the recurrent/progressive disease setting in brain metastases from NSCLC, post-XRT, at least 83 patients have been treated, with response rates ranging from 0 to 20%.

1.6.2 Clinical Setting 2: Trials in which temozolomide is used as a single agent without radiotherapy. In general, these trials have included patients with multiple histologies, and overall response rates have been modest; for non-small cell lung cancer brain metastases in particular, the response rate is 24% in 21 NSCLC patients. The key study using temozolomide in this context is summarized below:
Siena, et al: ASCO Proc, 2003 abstract # 407; overall response rate with temozolomide was 24% in 21 NSCLC patients with newly diagnosed brain metastases from NSCLC.[69]
Some of these responses are dramatic, as demonstrated in a case report by Biasco, et al, (*NEngJMed* 345:621-2, 2002) [70] which demonstrated complete response of melanoma brain metastases when treated with six cycles of temozolomide.
In summary, in the newly diagnosed, previously untreated setting of brain metastases from NSCLC, 21 patients have been treated, with a response rate of 24%.

1.6.3 Clinical Setting 3: Trials in which temozolomide is used as an adjunct with whole brain radiotherapy (WBRT). In general, these trials have included patients with multiple histologies, the bulk of which (approximately 80% are patients with NSCLC) and overall response rates significantly higher for temozolomide plus radiotherapy, and other clinical endpoints such as functional outcomes and survival also trending favorably for the temozolomide plus WBRT arms; for non small cell lung cancer brain metastases in particular, response rates have ranged from 35-96%. The key studies using temozolomide in this context are summarized below:
Dardoufous, et al: Proc ASCO 2001, abstract # 2048; overall response rate with temozolomide plus WBRT was 81% in 11 NSCLC patients with newly diagnosed brain metastases.[71]
Antonadou, et al: *JCO* 20:3644-50, 2002; in this randomized Phase II trial, 48 patients were enrolled, 40 with lung cancer, of whom 31 had NSCLC and the allocation by arm was 15 to WBRT alone and 16 to WBRT plus temozolomide. The overall response rate with temozolomide plus WBRT was 96% compared to 66% with WBRT alone (p=0.017). In this study, functional assessment was conducted using a 3-tiered scale (I: fully functional, able to work; II: fully functional, unable to work; III: bedridden); at baseline, 26% and 24% of patients were level I in the WBRT and the WBRT plus temozolomide arms, respectively. Post-treatment, 38% and 46% of patients were level I in the WBRT and the WBRT plus temozolomide arms, respectively; the magnitude of functional improvement was therefore much greater in the combination arm.[72]
Verger, et al: *Proc ASCO* 2003, abstract #404: in this randomized Phase II trial, 83 patients were enrolled, approximately half (~40 with non small cell lung cancer, of whom there was balanced allocation by arm (WBRT alone vs. WBRT plus temozolomide). The overall response rate at day 90 favored the combined arm (39 vs 25%); death from CNS progression was higher in the WBRT alone arm (69 vs 41%, p =0.029); median survival trended favorably for WBRT plus temozolomide (17 vs. 23 weeks).[73]

Antonadou, et al: *Int J Radiat Oncol Biol Phys* 54:93 2002; in this randomized Phase III trial (separate from the above mentioned Phase II randomized trial by the same author), 134 patients were enrolled, 82% with non-small cell lung cancer.[74] The overall response rate was statistically and clinically superior with temozolomide plus WBRT at 53% compared to 33% with WBRT alone. Several other endpoints were also evaluated in this trial and all favored the combination arm. These are illustrated below; please note that survival in the combination arm was 7.9 months compared to 4.3 months with WBRT (which, parenthetically is exactly what would be predicted from all the major brain metastases trials in terms of WBRT survival); the p value was .06; the magnitude of survival improvement is 84%, and clearly, with an adequately powered study would have reached statistical significance. Importantly, and confirming the findings in the Verger trial, the CNS death rate was lower in the combination arm (13 vs. 28%, p = 0.034) and steroid independence was also greater for the combination arm (85 vs 49% at 3 months, p = 0.002). {data presented at ASTRO 2002 Annual Meeting}

	WBRT + TMZ	WBRT	p
3 mo RR	53%	33%	.02
3 mo steroid independence	85%	49%	.002
CNS death	13%	28%	.034
Median TTP	7.5 mo	6 mo	.011
Median Survival	7.9 mo	4.3 mo	.06

In summary, in the newly diagnosed disease setting in brain metastases from NSCLC, temozolomide plus XRT, (in approximately 276 patients) response rates with the combination arm are consistently superior to WBRT alone and in all the randomized trials (Phase II and III), survival also favors the combination arm but does not reach statistical significance due to inadequate numbers in each individual trial.

1.6.4 Clinical Setting 4: Trials in which temozolomide is used as a salvage agent for non-small cell lung cancer, without brain metastases. The key studies using temozolomide in this context are summarized below:

Adonizio, CS, et al: *Clin Lung Cancer* 3:254-8, 2002[75]; *Ann Oncol*, 12:249-254, 2001: In this phase II trial of temozolomide in previously treated patients with non-small-cell lung cancer, preliminary results in 38 patients showed 3 responses and 12 stable disease with an overall median survival of 8.1 months (95% {CI] 3.8-14.8 months) In this regard, it is of interest to note that docetaxel as salvage therapy in phase III studies had response rates of 6-12% with a median survival 6-17 months (Shepherd FA, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 18:2095-2103, 2000[76] and Fossella FV, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 18: 2354-62, 2000.)[77]

Antonadou D, et al [78] (personal communication; unpublished, ongoing Phase II trial): In this study, 22 patients with Stage III squamous cell lung cancer have been treated with temozolomide 75 mg/m^2/d x 6 wk with concurrent thoracic XRT to 60 Gy, then 200 mg/m^2 x5 d, q 28d x 6. Responses were assessed by CT 2 months after completion of XRT; there were 2 CR, 12 PR, 4 SD and 4 PD, for an overall response rate of 14/22 (64%).

Three Phase 2 studies in subjects with metastatic colorectal cancer (P00347), prostate (P00348), or non-small cell lung cancer (NSCLC) (P00349) were conducted using a temozolomide oral dosing regimen consisting of 7 days of dosing at 150 mg/m2/day of temozolomide followed by 7 days with no dosing. (Doc ID 2112193. A Phase II study of temozolomide (SCH 52365) in the treatment of patients with metastatic colorectal carcinoma (study report for Protocol No. P00347). Kenilworth (NJ): Schering-Plough Research Institute;

FEB 2003/ Doc ID 2322178. A Phase II study of temozolomide (SCH 52365) in the treatment of patients with metastatic prostate cancer (study report for Protocol No. P00348). Kenilworth (NJ): Schering-Plough Research Institute; APR 2003/ Doc ID 2089871. A Phase II study of temozolomide (SCH 52365) in the treatment of patients with metastatic non-small cell lung cancer (study report for Protocol No. P00349). Kenilworth (NJ): Schering-Plough Research Institute; MAR 2002.

This dosing regimen was then repeated until disease progression or discontinuation due to toxicity for a maximum of 6 months (6 cycles). Subjects were to have failed only one prior chemotherapy treatment for metastatic cancer. The primary endpoint for each study was the response rate (complete and partial). Secondary endpoints included time to progression, overall survival, and changes in disease-related symptoms. In NSCLC subjects enrolled in Study P00349 (n=32), 7 of 32 subjects had stable disease as the best response, with 22 of 32 subjects having disease progression. Stable disease was sustained for a median of 4 cycles and a mean of 3.8 cycles. Three subjects did not have any response determinations due to discontinuation due to an AE (n=1) or reasons unrelated to the treatment (n=2).

In summary, in the recurrent/progressive disease setting in NSCLC, temozolomide demonstrates modest activity, comparable to that achieved with Docetaxel.

1.6.5 Clinical Setting 5: Trials in which temozolomide is used in conjunction with other chemotherapy. This is summarized in Section 9.3.2.

1.6.6 Toxicity of Cranial Radiation and Temozolomide

Temozolomide has been extensively used, both in (RTOG 9813) and out of the clinical trial setting, with 60 Gy cranial radiotherapy in hundreds, if not thousands of brain tumor patients (including, but not limited to glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, etc.). Therefore, there should be no major unanticipated safety concerns in this trial.

Taken collectively, these data from at least 12 clinical trials provide support for the temozolomide arm of this phase III study.

1.7 Gefitinib

1.7.1 Laboratory Support for Combining Radiation and EGFR Inhibitors

Recently, a substantial body of literature has emerged in the preclinical arena supporting the general concept of combining EGFR inhibitors and radiotherapy, including, but not limited to Iressa. This body is too large to summarize briefly here but has recently been reviewed by Harari and Huang.[79] For illustrative purposes and to answer the questions raised regarding potential interactive mechanisms, we have expanded briefly on some of these reports. Huang and colleagues evaluated the antitumor activity of gefitinib in combination with radiation in human squamous cell carcinomas (SCCs) of the head and neck (H&N). Gefitinib produced a dose-dependent inhibition of cellular proliferation in human SCCs grown in culture. Flow cytometry analysis of cell cycle progression confirmed the accumulation of cells in G1 phase following exposure to gefitinib. Clonogenic analysis demonstrated that treatment of SCCs with gefitinib reduced cell survival following radiation exposure. Flow cytometric analysis further demonstrated that treatment of SCCs with gefitinib amplified radiation-induced apoptosis. Tumor xenograft studies confirmed that oral administration of gefitinib, or focal radiation, resulted in partial and transient tumor regression in both SCC-1 and SCC-6 xenografts. In contrast, profound tumor regression and re-growth delay was observed in mice treated with the combination of gefitinib and radiation. To examine anti-angiogenic effects, they studied the impact of gefitinib on human umbilical vascular endothelial cells (HUVEC). In the presence of reconstituted Matrigel matrix, HUVEC cells established a capillary-like network structure (tube formation). Treatment with gefitinib reduced the cell-to-cell interaction of HUVEC cells, resulting in disruption of tube formation. The effect of gefitinib was further examined using an *in vivo* tumor xenograft model of angiogenesis (Matrigel plug) in athymic mice. Systemic treatment with gefitinib significantly inhibited tumor-induced neovascularization across the Matrigel plug. Taken together, these results suggest that the antitumor activity of gefitinib in combination with radiation appears to derive from not only proliferative growth inhibition (with associated cell cycle arrest and enhancement of radiation-induced apoptosis), but also from inhibition of tumor angiogenesis.[80]

The effect of gefitinib on proliferation, apoptosis, and clonogenic survival after radiation was determined in vitro and in vivo, using athymic nude mice with established subcutaneous A431 xenografts treated with either a single 10 Gy fraction or 4 daily 2.5 Gy fractions of radiation with or without gefitinib to determine effects on tumor growth delay. Treatment of A431 cells with

gefitinib in vitro reduced proliferation, increased apoptosis, and reduced clonogenic survival after radiation. Strikingly greater than additive effects of gefitinib in combination with radiation on tumor growth delay were observed in vivo after either a single 10 Gy fraction (enhancement ratio: 1.5) or multiple 4 x 2.5 Gy fractions (enhancement ratio: 4). Gefitinib reduced tumor vascularity, as well as levels of vascular endothelial growth factor (VEGF) protein and mRNA induced by stimulation with epidermal growth factor (EGF), suggesting a possible role of inhibition of angiogenesis in the effect. These data provide preclinical rationale for clinical trials of EGFR inhibitors including gefitinib in combination with radiation.[81]

Further rationale for evaluating the combination of ionizing radiation and selective EGFR tyrosine kinase inhibitors such as gefitinib in cancer patients comes from a recent study using gefitinib with ionizing radiation in human colon (GEO), ovarian (OVCAR-3), non-small cell lung (A549 and Calu-6), and breast (MCF-7 ADR) cancer cell lines. The antitumor activity of this combination was also tested in nude mice bearing established GEO colon cancer xenografts. With ionizing radiation or gefitinib, a dose-dependent growth inhibition was observed in all of the cancer cell lines growing in soft agar. A cooperative antiproliferative and proapoptotic effect was obtained when cancer cells were treated with ionizing radiation followed by gefitinib. This effect was accompanied by inhibition in the expression of the antiapoptotic proteins bcl-xL and bcl-2, and by a suppression of the activated (phosphorylated) form of akt protein. Treatment of mice bearing established human GEO colon cancer xenografts with radiotherapy (RT) resulted in a dose-dependent tumor growth inhibition that was reversible upon treatment cessation. Long- term GEO tumor growth regressions were obtained after RT in combination with gefitinib. This resulted in a significant improvement in survival of these mice as compared with the control group ($P < 0.001$), the RT-treated group ($P < 0.001$), or the gefitinib-treated group ($P < 0.001$). The only mice alive 10 weeks after tumor cell injection were in the RT-plus-gefitinib group. Furthermore, 10% of mice in this group were alive and tumor-free after 26 weeks. Similar results were obtained in mice bearing established human A549 lung adenocarcinoma xenografts. Finally, the combined treatment with RT plus gefitinib was accompanied by a significant potentiation in the inhibition of transforming growth factor alpha, vascular epidermal growth factor, and basic fibroblast growth factor expression in cancer cells, which resulted in significant antiangiogenic effects as determined by immunohistochemical count of neovessels within the GEO tumors.[82]

At the present time, it is not possible to predict which patients will respond to Iressa and which ones will not and whether information exists regarding expression of EGFR on brain metastases from NSCLC. Just as it is currently not possible to predict with accuracy exactly which patients will respond to radiation or chemotherapy, it is also not possible to predict who will respond to EGFR inhibitors. There was early speculation regarding a large number of putative predictive markers for anti-EGFR therapies, including EGFR expression; none of these markers have consistently been successful at predicting responsive tumors, including overexpression of EGFR or not. Whereas this situation is less than ideal, it represents current scientific and clinical reality. This trial is not designed to solve this overarching question of identifying predictive markers for anti-EGFR therapies, and in fact this question is unlikely to be answered easily in the near future by any single trial. The absence of an answer to this question, however, should not be the rationale for further investigational trials of anti-EGFR therapies, just as the absence of predictive markers for chemotherapy or radiotherapy has not halted the exploration of Phase III concepts of these treatments.

Taken collectively, this extensive body of preclinical evidence suggests that anti-EGFR therapies in combination with radiotherapy are synergistic, possibly significantly more so than the experience with combining these approaches with chemotherapy. In particular, several investigators have specifically evaluated Iressa in this context and many of these models utilized NSCLC cell lines. No single predictive molecular marker for the activity of Iressa or any other anti-EGFR strategy has been identified to date, including EGFR expression.

1.7.2 Clinical Efficacy of Iressa in NSCLC with Brain Metastases

There is growing literature to support Iressa in the treatment of NSCLC, particularly in the context of brain metastases. That literature is summarized as follows.

There is preliminary evidence that gefitinib may cross the blood-brain tumor barrier and confirmatory investigations are underway.[83]

Phuphanich and colleagues[84] reported a response with gefitinib as a single agent in non-small cell lung cancer and multiple recurrent brain metastases. Clearly, anecdotal as this may seem, this report provides clinical evidence for activity as well as the ability to cross the BBB in the presence of brain metastases.

Recently, Cappuzzo, et al, have reported 4 additional cases of brain metastases from NSCLC treated with and responding to Iressa[85]. These patients were enrolled on the gefitinib compassionate use protocol by the author. Two patients had received prior WBRT for brain mets and at progression received gefitinib; the other 2 received gefitinib as sole therapy for brain metastases. No other systemic therapy was delivered concurrently, and all 4 brain metastases patients experienced a PR; the progression-free duration was 8, 15, 6+, and 11+ (+ implying no progression at the time of the report) months. Although modest in patient number, sustained progression-free durations of this length are not a trivial clinical outcome. Parenthetically, all 4 patients also experienced neurologic improvement while on gefitinib. Further, at ASCO 2003, this group provided data on 27 patients with brain metastases from NSCLC treated with gefitinib. The aim of their study was to evaluate the efficacy and safety of gefitinib as second or third line treatment in NSCLC patients with brain metastases. Even in this extensively and heavily pretreated group (20 patients had received prior platinum-based chemotherapy and 11 had received WBRT and progressed), the response rate in the first 20 patients (with adequate follow-up for assessment) was 30% PR and 25% SD, for an overall clinical benefit of 55%.[86]

Gelibter, et al[87] recently described results derived from the Compassionate Use Program of Iressa; out of 11 patients with brain metastases from NSCLC, 2 responses were seen and they also experienced symptomatic improvement. These patients were heavily pretreated, with platinum-based chemotherapy. Other investigators have also reported case reports of responses in 4 brain metastases patients with NSCLC treated with Iressa as a single agent [88,89]

Regarding Iressa's activity in NSCLC, as CTEP is well aware, Douillard, et al.[90] reported that the response rate for 210 patients, randomized between a dose of 250 or 500 mg a day, was 18.4 % and 19% respectively; the disease control rates for these doses were 54.4% and 51.4% respectively. Median follow-up at the time these data were reported was 6.3 months. Additionally, a prospectively defined improvement in disease related symptoms was seen in 40% (250 mg dose level) and 37% (500 mg per day) for these patients. In a second study[91], 216 patients also received gefitinib as a monotherapy. These patients were also randomized to 250 and 500 mg per day. These patients, as was the case in the Douillard study, were heavily pretreated. The symptom improvement rate was 43.1% for 250 mg/day and 35.1% for 500 mg/day respectively. A correlation was observed between symptom improvement and objective response at both dose levels.

The results of the INTACT Trials I and II (announced by Astra-Zeneca in 8/02) indicated that there was no added clinical benefit when gefitinib was combined with two standard chemotherapy regimens (gemcitabine with cisplatin and paclitaxel and carboplatin) in non-small cell lung cancer. However, the IDEAL I and II trial results were positive, indicating that gefitinib as monotherapy following chemotherapy had an objective tumor response rate of 18.2% and 11.6% respectively. Based on these data, gefitinib has been approved as a third line drug for non-small cell lung cancer.[91]

Taken collectively, this body of clinical evidence suggests that Iressa as a single therapy is active in NSCLC, yielding definitive clinical responses and symptomatic improvement. In particular, there are now emerging reports of clinically validated responses in progressive brain metastases from NSCL treated with Iressa; although these numbers are small, the activity is real and clinically impressive. No single predictive molecular marker for the activity of Iressa or any other anti-EGFR strategy has been identified to date from the clinical trials, including EGFR expression.

1.7.3 Toxicity of Gefitinib in Patients with Brain Metastases

The safety of Iressa in NSCLC, particularly in the context of brain metastases treated with radiosurgery is an important issue. Although Iressa and whole brain radiotherapy has not been piloted in brain metastases patients, the RTOG has combined brain irradiation to a target dose of 60 Gy in its current Glioblastoma Multiforme study (RTOG 0211). To date 88 patients have been entered on study with no obvious Iressa/radiation complications. Typically these patients have very large volumes of brain irradiated, and the 60 Gy dose is substantially higher than the

37.5 Gy proposed in this trial; also, the Iressa dose in this trial is lower than the escalation of Iressa dose occurring in RTOG 0211.
Accordingly, the investigators believe the use of Iressa in combination with cranial radiotherapy (in GBM patients) does not adversely affect the safety profile.

In summary, these data support the gefitinib arm of this clinical trial in patients with brain metastases receiving radiation therapy.

1.8 Quality of Life

Quality of Life has become recognized as a critical endpoint in clinical oncology trials.[92] This is particularly the case in the setting of patients with a difficult prognosis, such as lung cancer patients with brain metastases, for whom the median survival is approximately 6 months. QOL provides patient-derived information by which to analyze the delicate balance between the potential for improved survival and increased toxicity with experimental therapies. There is little prospective quality of life data on patients with brain tumors or metastases. In this general setting, one such validated questionnaire is the Functional Assessment of Cancer Therapy-Brain (FACT-Br) instrument. Weitzner demonstrated that the validity and reliability of this instrument were high and that the brain subscale tests substantially different QOL issues than the general core instrument. [93]

A key issue relates to how to interpret a clinically meaningful change in QOL. Using the FACT-L (FACT – lung) instrument, which was previously found to be a reliable and valid questionnaire in patients with lung cancer. [94] Cella et al. more recently set out to measure a clinically meaningful change (CMC) utilizing this instrument.[95] They found that the minimum clinically relevant change was estimated to be 2-3 points (or 5% change) for the Lung Cancer Subscale (LCS), a 7-item questionnaire assessing symptoms commonly reported by lung cancer patients. Their estimates compared favorably with those of the EORTC-QLQ instrument, which specifies a 5-point standard for meaningful change using scores transformed to a 100-point scale (i.e. 5%). Based on the similarity of these estimates across two widely used instruments, Cella et al. suggest that a between-group difference or longitudinal change of 5% of a full scale range may be considered a minimally important change. As this is a study of patients with brain metastases, the most relevant questions are those found on the FACT-Br subscale, a total of 23 questions. The maximum score on the FACT-Br subscale is 92, such that a change of 5 points on this scale would represent the minimal clinically meaningful change (CMC). As this subscale has not been validated on its own, the general FACT-G questionnaire will be collected at key time points as well. Moreover, as these patients have lung cancer and the systemic therapy may also impact on the lung cancer symptoms, we will also collect the Lung Cancer Subscale (LCS), which has been separately tested and found to be clinically relevant.[96] To reduce the burden on patients, these questionnaires will be collected only at selected time points as delineated in Section 11. The average time to completion of the FACT-G instrument is 5-10 minutes, and even less for the stand alone symptom subscales.

In addition to collecting prospective quality of life data, this study will also utilize the Quality-Adjusted Life Year (QALY) approach. The QALY approach assigns to each period of time a value corresponding to the HRQOL during that period. Utilities are the numerical judgments of the desirability of a set of outcomes and range from a value of 0 (representing death) to 1 (representing perfect health). Utilities can be measured by a variety of techniques ranging from Time Trade Off (TTO) to the Heath Utilities Index III or EQ-5D.

The EQ-5D is a method for obtaining valuations of health-related quality of life. It can also be used as an adjustment to survival and in cost-utility analysis. It is a two-part questionnaire that takes approximately 5 minutes to complete.[97] The first part of the EQ-5D consists of 5items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problems, 2-moderate problems and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 (3 to the 5th) health states to which unconsciousness and death are added.[98] The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm 10 point-interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale and best imaginable health state is scored

as 100 at the top. Both the 5-item index score and the VAS score are transformed into a utility score between 0 "Worst health state" and 1 "Best health state". Either the index score or the VAS score can be used in the quality adjusted survival analysis, or enter the cost-utility equation, depending on the health state(s) of interest.[99]

Quality adjusted survival is the weighted sum of different time in different health states added up to a total quality-adjusted survival time [U= sum of quality (qi) of health states K times the duration (si) spent in each health state.[100]

Although developed in Europe, the EQ-5D has been used in the United States and Canada.[101-104] There are no published reports of the EQ-5D's use in the evaluation of patients with brain metastases, but it has been used in patients with a variety of other neurologic conditions.[105-108] Trippoli et al. compared the EQ-5D to the 36-item Short Form health survey (SF-36) in assessing quality of life in patients with non-small cell lung cancer.[1094,110] They found strong correlation in the measurements produced by the two forms.

Quality-Adjusted survival as measured by QALY is important in health policy. It allows by means of a single value, the QALY, comparison of treatments for entirely different diseases. Quality of life measurements, while giving information regarding the outcome of treatment of patients with a specific disease, does not allow for comparison of different diseases. Health policy analysts could then rank order treatments from greatest amount of QALYs to least. Using QALYs will also allow for future economic analyses.

We hypothesize patients treated with WBRT + SRS + gefitinib will have the largest QALYs by virtue of having the greatest tumor control and minimal tumor induced morbidity.

1.9 Summary

Based on the above data, the RTOG will employ WBRT + SRS as the standard treatment for patients with non-small cell lung cancer and 1-3 brain metastases and will attempt to further improve on the results of RTOG 9508 by investigating two promising drugs, temozolomide and gefitinib, in conjunction with WBRT + SRS in a three-arm clinical trial.

2.0 OBJECTIVES

2.1 To determine if either temozolomide or gefitinib combined with WBRT and SRS improves survival compared to WBRT and SRS alone.

2.2 To compare the effect of the treatment regimens on the following secondary endpoints (the results of the primary endpoint analysis will determine which treatment arms will be of interest to compare for the secondary endpoint analyses): time to CNS progression, quality-adjusted survival, change in quality of life (FACT-Br subscale) at 3 months, change in performance status at 6 months, change in steroid dependence at 6 months, and cause of death (neurologic vs. other).

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Histologically confirmed non-small cell lung cancer with the presence of 1-3 intraparenchymal brain metastases.

3.1.2 A diagnostic contrast-enhanced MRI demonstrating the presence of 1-3 brain metastases performed within two weeks prior to registration.

3.1.3 The contrast-enhancing intraparenchymal brain tumor must be well circumscribed and must have a maximum diameter of ≤ 4.0 cm in any direction on the enhanced scan. If multiple lesions are present and one lesion is at the maximum diameter, the other(s) must not exceed 3.0 cm in maximum diameter.

3.1.4 Patients who present with symptoms of brain metastases at the time of initial diagnosis are eligible and do not need to demonstrate one month of stable scans.)

3.1.5 Age 18 years or older.

3.1.6 Zubrod 0-1

3.1.7 Neurologic Function Status 0, 1, or 2. (Appendix III)

3.1.8 Patients may have stable extracranial metastases.

3.1.9 Contrast-enhancing CT scans of the chest, abdomen and pelvis, and bone scan to determine the extent of extracranial malignant disease.

3.1.10 Adequate bone marrow reserve (hemoglobin ≥ 8 grams, absolute neutrophil count ≥1000/mm3, platelets ≥ 100,000/mm3); all liver function tests (AST/SGOT, alkaline phosphatase, total bilirubin, LDH) < 2 x institutional upper limit of normal (uln); serum creatinine < 1.5 x uln. Serum pregnancy test (in patients in whom conception is possible) must be done within 24 hours prior to randomization.

3.1.11 Patients randomized to receive gefitinib who are on enzyme inducing seizure medicines including phenytoin, carbamazepine, rifampicin, barbiturates must be converted to a non-enzyme inducing anti-seizure medication. Patients on Arm 3 will not be able to start treatment immediately if converting. See Section 9.4. See Appendices VII and VIII.

3.1.12 All patients on anticoagulants must be monitored closely—at least monthly.

3.1.13 Patient must sign a study-specific informed consent form. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the patient's legal representative.

3.2 Conditions for Patient Ineligibility

3.2.1 Major medical illnesses or psychiatric impairments, which in the investigator's opinion will prevent administration or completion of the protocol therapy and/or interfere with follow-up.

3.2.2 All patients who have undergone a complete resection of all known brain metastase(i)s. Patients who have undergone subtotal resection are eligible providing residual disease is =/< 4.0 cm in maximum diameter.

3.2.3 Inability to obtain histologic proof of non-small cell lung cancer.

3.2.4 Patients with leptomeningeal metastases documented by MRI or CSF evaluation.

3.2.5 Clinical or radiographic evidence of progression (other than the study lesion(s)) within one month prior to enrollment. (Patients who have brain metastases at initial presentation are eligible and do not need to demonstrate one month of stable scans.)

3.2.6 Patients with metastases within 10 mm of the optic apparatus so that some portion of the optic nerve or chiasm would be included in the high dose SRS boost field.

3.2.7 Patients with metastases in the brainstem, midbrain, pons, or medulla.

3.2.8 Patients with liver metastases.

3.2.9 Previous cranial radiation.

3.2.10 Women who are pregnant or nursing are not eligible as treatment involves unforeseeable risks to the fetus or child.

3.2.11 Patients who are HIV positive are not eligible.

3.2.12 Any evidence of clinically active interstitial lung disease (patients with chronic stable radiographic changes who are asymptomatic need not be excluded).

3.2.13 Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment.

3.2.14 Concomitant use of St. John's Wort.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS (IN ADDITION TO REQUIRED EVALUATIONS IN SECTION 3.0)

4.1 Complete history and physical examination with a detailed neurological examination.

4.2 The Quality of Life forms must be obtained pre-randomization so that they may be completed by the patient at the appropriate time points (see Section 11.1). They are available on the RTOG website www.RTOG.org

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements

The treating facility must complete and submit the stereotactic radiotherapy facility questionnaire for RTOG approval (Appendix VI). The facility's questionnaire must be approved by RTOG prior to enrollment of any patients. Allow adequate time for processing. Prior approval for RTOG 93-05 or 95-08 is acceptable. Institutions without radiosurgery capability may refer a patient to an RTOG approved-RT facility.

Each institution must submit a Study Agent Shipment Form (Appendix IV) to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case (the shipment form is only submitted once). Allow adequate processing time (7-10 days) before calling to register the first case.

The Quality of Life forms must be obtained pre-randomization so that they may be completed by the patient at the appropriate timepoints (see Section 11.1). They are available on the RTOG website www.RTOG.org

5.2 Registration

Patients can be registered only after eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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/RTOG audit.

6.0 RADIATION THERAPY

6.1 Whole Brain Radiation Therapy: NOTE: Intensity Modulated (IMRT) is not allowed.

6.1.1 Total Dose: Whole brain radiation therapy (WBRT) must begin within one week of randomization. One treatment of 2.5 Gy will be given daily 5 days a week for 3 weeks, for a total of 37.5 Gy. Both portals shall be treated during each treatment session.

6.1.2 Physical Factors: Treatment will be delivered using megavoltage machines with photon beams ranging from 4 to 8 MV. The minimum dose rate at the midplane in the brain on the central axis must be 0.50 Gy/minute. Electron, particle, or implant therapy is not permissible.

6.1.3 Simulation, Immobilization, Localization: The patient will be treated in the supine position. Adequate immobilization and reproducibility of position must be ensured. The target volume will cover the brain and the meninges to the foramen magnum.

6.1.4 Treatment Planning: Treatments must be delivered through parallel opposed or 5 degree RAO-LAO fields that cover the entire cranial contents. There should be beam fall-off of at least 1 cm. The eyes will be excluded from the beam either by field arrangement or shielding.

6.1.5 Dose Specification: Doses will be specified at the central axis at midplane on the brain

6.2 Stereotactic Radiosurgery

The treating facility must complete and submit for RTOG approval the RTOG stereotactic radiotherapy facility questionnaire. The facility's questionnaire must be approved by RTOG prior to enrollment of any patients. Prior approval of this institution questionnaire for RTOG 93-05 or 95-08 is sufficient. The Stereotactic Radiotherapy Guidelines (Shaw et al.)[111] are available from on the RTOG website (see Appendix V).

6.2.1 It is possible at the time of radiosurgery that one of these scenarios occurs:

- An identified metastasis at the time of enrollment now exceeds the acceptable upper limit diameter (4.0 cm for a solitary metastasis, or 3.0 cm for multiple metastases). Any such lesion should not be treated with SRS.
- If additional lesions exist at the time of radiosurgery, radiosurgery should be delivered to the three largest treatable lesions that meet the eligibility criteria. The physicians submitting the films should circle and number each lesion (1-3) with a wax pencil, in accordance with the numbering of lesions at baseline, so each lesion can be uniformly identified and the response to treatment can be evaluated for each corresponding lesion.
- If the lesions are not visualized after WBRT, radiosurgery should not be delivered.

6.2.2 Timing: Radiosurgery must be delivered within 14 days of the completion of WBRT.

6.2.3 Total Dose Determination: The total dose is dependent on the size of the metastatic lesion(s) as follows:

Maximum Tumor Diameter	*Assigned Dose*
< 2.0 cm	24 Gy
2.1-3.0 cm	18 Gy
3.1-4.0 cm	15 Gy

6.2.4 SRS Technique: All participating institutions must use FDA-approved stereotactic localization procedures for imaging procedures and treatment delivery, perform target localization using CT or MRI data, and have a treatment planning system capable of generating isodose distributions in three dimensions for a given treatment.

6.2.5 Target Volume Determination:

6.2.5.1 Target volume and isocenter determination will be based on a contrast-enhanced CT or MRI (or by CT-MRI fusion) scan with the patient's head in a stereotactic frame. The imaging study used to deliver the radiosurgical treatment must be the same as used to determine size of the metastatic lesion(s).

6.2.5.2 Stereotactic CT or MRI slice thickness may not exceed 3 mm.

6.2.5.3 The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

6.2.6 Dose Prescription and Dosimetry Requirements

6.2.6.1 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 100% (maximum) dose will be recorded for each patient. The prescription dose shall be delivered to the 50-90% (maximum = 100%) isodose surface, and is defined as the minimum dose to the target volume. The minimum dose shall be established by the SRS treatment planning software or by an examination of the dose distribution on each axial level on which the target volume has been defined, and/or by the target dose-volume histogram.

6.2.6.2 For patients with two or three brain metastases, each lesion will be assigned to a SRS dose level according to its maximal diameter. If any two lesions are within 0.8 to 2 cm of each other, the intervening midplane dose will not exceed 13.0 Gy. This dose may represent a dose to each respective target that will be less than the dose prescription listed in Section 6.2.3. A second stipulation will involve size. If one lesion is > 3.0 cm the remaining two metastases may not exceed 3.0 cm each in diameter. This stipulation is designed to minimize toxicity in patients with larger volume multiple metastases. A review of patient and tumor criteria among patients entered into RTOG 91-04, a phase III trial for patients with unresected brain metastase(i)s, would suggest that the majority would meet the entry criteria of this trial.

6.2.7 Radiosurgery Treatment Planning Data

6.2.7.1 Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion in the transverse, coronal, and sagittal planes.

6.2.7.2 The isodose distributions on the required three planes for each target lesion will include isodose lines (in % dose) that represent 10% dose increments.

6.2.7.3 Dose-volume data for accumulated volumes within the target and within the treated volume must be submitted. The data should be recorded in 1 or 2 Gy increments. If the prescription dose is 15 Gy and 2 Gy increments are used to report dose-volume data, then the volume receiving 15 Gy should be additionally reported.

6.3 Recommended Salvage Therapy for Progression within the Brain

6.3.1 If there are 1-3 new brain metastases on the follow-up MRI, SRS should be given to the new lesions.

6.3.2 Other salvage therapy at the discretion of the treating physician.

6.3.3 The dates and type of all salvage therapy must be reported to RTOG Headquarters within one week of such therapy.

6.3.4 If the patient undergoes salvage craniotomy, enhanced brain MRI and either MR Spectroscopy or PET scan is recommended pre-operatively. Reports of pathology from any salvage craniotomy and the above scans should be submitted.

6.4 Critical Structures

The dose to the optic nerves, optic chiasm and brainstem should not exceed 800cGy from the SRS. The dose to the motor strip should not exceed 1500cGy from the SRS.

6.5 Documentation Requirements

See Section 6.2.7.

6.6 Compliance Criteria

A final review of the stereotactic radiotherapy treatment will be performed by the protocol chairman and the protocol physicist. The review process will evaluate the Radiosurgery Summary Form, diagnostic CT, and the stereotactic CT/MRI (or a hard copy thereof) with superimposed isodoses at required levels. Based on the evaluation and verification of data submitted, the following Quality Assurance scores will be assigned to each case.

6.6.1 Lesion Identification

The physicians submitting the films should circle and number (1-3), with wax pencil, each lesion so the radiosurgery parameters can be evaluated for the corresponding lesion.

6.6.2 Isodose QA

Three isodose lines should be submitted: the prescription isodose line, 90% of the prescription isodose line (not 90% of total dose) and 80% of the prescription isodose line, should be submitted. See Appendix V.

6.6.3 Target Coverage QA

Per protocol: The submitted 90% isodose line (90% of the prescription dose, not total dose) completely encompasses target.

Acceptable variation: 80% isodose line covers the target.

Unacceptable deviation: 80% isodose line does not cover target.

6.6.4 Dose QA

Per protocol: If the maximum dimension of the tumor is

< 2.0 cm: 24 Gy

2.1-3.0 cm: 18 GY

3.1-4.0 cm: 15 Gy prescribed to the isodose line that encompasses the target.

Unacceptable deviation: Anything else

6.6.5 Dose Homogeneity QA

The ratio of the maximum dose to the prescribed dose *(MD/PD)* is:

Per protocol if ≤ 2

Acceptable variation if > 2 but ≤ 2.5

Unacceptable deviation if > 2.5.

6.6.6 Dose Conformity QA

The ratio of prescription isodose volume to the target volume *(PI/TV)* is:

Per protocol if between 1.0 and 2.0

Acceptable variation if ≥ 0.9 but < 1.0 or >2.0 but ≤ 3.5.

Unacceptable deviation if > 3.5.

(The prescription isodose volume may be obtained from the dose volume histogram, which must be submitted in tabular, not graphic, form or by measuring the area of the prescription isodose on sequential levels. See Appendix V.)

6.6.7 Overall Radiosurgery Q/A Score

The ration of prescription isodose volume to the target volume *(PI/TV)* is:

Per protocol if no variations or deviations are scored.

Acceptable if no variations are scored.

Unacceptable if a deviation is scored.

6.7 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Paul Sperduto, M.D. and Michael Schell, Ph.D. will perform an RT Quality Assurance Review within 3 months after the study has reached these accrual targets or as soon as complete data for the sampled cases has been reviewed at RTOG Headquarters, whichever occurs first. These reviews will be on going and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

6.8 Radiation Adverse Event Reporting — RTOG AE TELEPHONE LINE (215) 717-2762

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). **Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.**

6.8.1 Life-threatening and Grade 4 Events

All life-threatening events (events, which in view of the investigator, place the patient at immediate risk of death from the reaction) or Grade 4 events that are definitely, possibly, or probably related to protocol treatment using radiation therapy must be reported by telephone to the RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762, or to 1-800-227-5463, X4189, to the RTOG Group Chair, and to the Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

6.8.2 Fatal Events (Grade 5)

All deaths with the attribution of definitely, possibly, or probably related to protocol radiation therapy must be telephoned to the RTOG Headquarters AE telephone line, (215) 717-2762, or 1-800-227-5463, X4189, to the RTOG Group Chair, and to the Study Chair within 24 hours of discovery. Sites are responsible for local reporting of adverse events as required by their IRB.

All deaths during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone within 24 hours of discovery to the RTOG

Headquarters AE telephone line at (215) 717-2762 or 1-800-227-5463, X4189. If the event is more than 30 days from completion of radiation treatment, but is felt to be definitely, possibly, or probably resulting from protocol radiation therapy, this event should be telephoned to RTOG Headquarters using the same numbers as listed above.

6.8.3 Documentation

Arm 1

Radiation therapy is the only modality in Arm 1 of this protocol; therefore, serious adverse events are reported on the appropriate case report forms with a dictated summary of the event(s) from the Primary Investigator (A MedWatch form is not applicable for radiation therapy alone grade 4 and grade 5 events). These items must be sent to RTOG Headquarters within 10 working days of the telephone report.

Arms 2 and 3

Radiation therapy is combined with chemotherapy administration in Arms 2 and 3 of this protocol; therefore, ALL serious adverse events are reported using the appropriate reporting form (MedWatch/AdEERS) as stated in Section 7.0 of this protocol.

6.8.4 Summary of AE Reporting in Protocols Involving Radiation Treatment

Arm 1

- Report Grade 4/Grade5 AEs;
- Telephone report to RTOG within 24 hours of discovery;
- Use appropriate case report forms/dictated summary of events for documentation and send to RTOG HQ within 10 days (MedWatch/AdEERS not applicable);
- Institutional reporting as required;
- For DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT:
- Telephone report to RTOG within 24 hours of discovery;
- Appropriate case report forms and if indicated, dictated summary.

6.8.5 Arms 2 and 3

- Report Grade 4/Grade 5 AEs;
- Telephone report within 24 hours of discovery;
- Document using the appropriate report — MedWatch or AdEERS within 10 days (a dictated summary and CRF's may also be indicated);
- Institutional reporting as required;
- For DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT:
- Telephone report to RTOG within 24 hours of discovery;
- Follow guidelines outlined in Section 7.0 of this protocol for AE reporting.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Temozolomide

(See also Sections 1.6 and 9.3.2) See the package insert for further information.

7.1.1 Drug Information:[112]

Temozolomide belongs to a group of compounds known as imidazotetrazinones. Its chemical name is 3, 4-dihydro-3-methyl-4-oxoimidazo[5, 1-d]-as-tetrazine-8-carboxamide. The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyl-triazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

7.1.2 Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

7.1.3 Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and

9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

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

7.1.5 Special Populations

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

Caution should be exercised when Temodar is administered to patients with severe renal impairment. Temodar has not been studied in patients on dialysis.

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

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

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

7.1.5.5 Drug-Drug Interactions: In a multiple dose study, administration of temozolomide with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

Population Analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or Phenobarbital on the clearance of orally administered temozolomide.

7.1.6 Known Potential Adverse Events

Adverse events to be monitored include myelosuppression (neutropenia, leukopenia and thrombocytopenia), fatigue, anorexia, nausea, vomiting. Secondary leukemia and/or myelodysplastic syndrome are less common.

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

7.1.6.2 Contraindications: Temozolomide is contra-indicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

7.1.6.3 Pregnancy Category D:

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide. Men should use adequate birth control and not father children while on the drug. Sexual partners of study participants must use adequate birth control measures to prevent pregnancy of a partner.**

7.1.7 Storage and Formulation

Temozolomide is supplied as a white, opaque, preservative-free, two-piece, hard gelatin capsule available in 250 mg, 100 mg, 20 mg and 5 mg strengths. Each strength is a different capsule size. The inactive ingredients for temozolomide capsules are lactose, anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

Temozolomide capsules are packaged in amber glass bottles containing either 5 or 20 capsules of 5 mg, 20 mg, 100 mg or 250 mg strengths. Packaging and labeling of temozolomide will be in accordance with Good Manufacturing Practice (GMP) for clinical trials. Each temozolomide label will indicate the dosage strength, number of capsules in each bottle, lot and/or PSR number(s), study number (RTOG and SPRI), storage conditions, and will contain a caution statement in compliance with local requirements.

Investigators and pharmacists should note that the clinical trial supplies may only be used for the clinical trial for which they are indicated. They must not be employed for any other trial, not even for temozolomide studies on another type of tumor, or for any other clinical use.

Temozolomide must not be repackaged at investigational sites; rather it must be dispensed to study subjects in the original packaging with the original labeling provided.

7.1.7.1 Storage: As a solid temozolomide is thermally stable and does not decompose when exposed to normal light conditions. The product label recommends storage between 2 C and 30 C.

Temozolomide must be stored in a secure hospital pharmacy according to storage conditions specified on the label. An expiration date and /or recertification information will be provided by Schering-Plough. Study drug must be stored in such a way that it cannot be mixed up or confused with other medications, like clinical trial supplies or medicines for routine clinical use. Strict recommendations will be made to the patients to keep temozolomide in a cool dry place in the original amber glass bottle. The patients will be asked to return unused medications in order to perform appropriate drug accountability and check on patient compliance.

7.1.7.2 Supply: Integrated Therapeutics Group, Inc., a subsidiary of Schering-Plough has agreed to supply temozolomide free of charge for patients entered into this study. The drug will be distributed by a vendor, I.V. Solutions, Inc., under contract to RTOG. Schering-Plough has not offered financial support nor has any provision been made to share data or study results with Schering-Plough. (10/06/04)

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record form. Temozolomide will be distributed by I.V. Solutions, Inc. The Study Agent Shipment Form must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case.

The patient-specific drug supply will not be shipped by I.V. Solutions, Inc. until the patient has been randomized. I.V. Solutions, Inc. generally ships drug Mondays through Thursdays.

For Canadian shipments, allow 7 to 10 days lead time. RTOG will notify I.V. Solutions, Inc. to initiate each of these shipments. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.
Unused supplies at the sites will be returned directly to I.V. Solutions, Inc. Additional questions about supply and delivery should be directed to:

Gary F. Mead, R.Ph, MHA
I.V. Solutions, Inc.
162 North Main Street
Old Forge, PA 18518
***(570)* 457-9201**
Fax *(570)* 457-0465

7.1.8 Treatment

7.1.8.1 Dose:

The dosing information should be recorded in the subject's medical records and in the case report form for each cycle and should include the exact total dose of study drug. Any standard system for calculating body surface area (BSA) is acceptable, e.g., computer, slide rule, hand held calculator, or tables.

The height and weight obtained at the baseline visit will be used to calculate the BSA unless patients experience a greater than or equal to 10% body mass change. Since capsules of study drug are available in 5, 20, 100, and 250 mg strengths, all doses will be rounded up to the nearest 5 mg to accommodate capsule strength. The exact dose administered will be recorded in the case report form (CRF). Each dose of study drug should be given with the least number of capsules. Study drug should be given with approximately eight ounces of water over as short a time as possible. Subjects should be instructed to swallow capsules whole and in rapid succession and to not chew capsules. If vomiting occurs during the course of treatment, no re-dosing of the subject is allowed before the next scheduled dose. Water is allowed during the fasting period.

7.1.8.2 Temozolomide During WBRT

Temozolomide will be administered orally, once a day, for 21 days at the start of WBRT (whole brain radiotherapy) at 75 mg/m^2/day. Temozolomide should be taken on an empty stomach. It should be administered at approximately the same time every day within and during each cycle. In general, patient tolerability is best when the drug is given at bedtime with a serotonin inhibitor one hour prior to temozolomide. Prophylactic antiemetics must be administered to all subjects prior to temozolomide administration. (Since this is an oral drug, episodes of emesis will result in under dosing.) Prophylaxis for pneumocystis carini, during the radiotherapy stage of the protocol for patients receiving temozolomide, or when the patients lymphocyte count drops below 300 is strongly recommended, e.g., double strength trimethoprim sulfamethoxazole PO BID Q Saturday and Sunday, or pentamidine 300mg IV or by inhalation Q 4 weeks.

7.1.8.3 Temozolomide After WBRT

Four weeks after completion of WBRT treatment, the patient will be treated at 200 mg/m^2/day for 5 days, if they have not received prior chemotherapy. For patients who have previously been treated with chemotherapy, the dose of temozolomide shall be 150 mg/m^2/day for 5 days. Treatment cycles shall be repeated every 28 days following the first daily dose of study drug from the previous cycle, for a minimum of 2 and maximum of 6 cycles post completion of radiation therapy. It should be administered at approximately the same time every day within and during each cycle. In general, patient tolerability is best when the drug is given at bedtime with a serotonin inhibitor one hour prior to temozolomide. Prophylactic antiemetics must be administered to all subjects prior to temozolomide administration. (Since this is an oral drug, episodes of emesis will result in under dosing.)

7.1.8.4 Treatment Criteria for Subsequent Cycles Beyond Cycle 2:

Four weeks following 2 cycles of temozolomide post-WBRT, patients may, at the discretion of the treating physician, either:
Discontinue temozolomide and not receive further chemotherapy;
Initiate any acceptable systemic chemotherapeutic regimen for non-small cell lung cancer; this selection may include:

- the continuation of temozolomide alone to a maximum of 6 cycles after radiation.
- the continuation of temozolomide in combination with the agents and in doses specified in Section 9.3.
- the discontinuation of temozolomide and the initiation of a standard non -small cell lung cancer chemotherapy regimen.

7.1.8.5 Criteria for Continuing Temozolomide:

The initiation of subsequent treatment will be based upon complete blood counts (CBC) obtained within 48 hours prior to starting the next treatment phase. If ANC is ≥ 1,200/mm^3 and platelet count is ≥ 100,000/mm^3, then repeat cycles may be administered according to the dose modification guidelines in Section 7.1.8.6; otherwise study drug administration must be delayed. Growth factors are allowed but cannot be used to induce elevations in neutrophil count for the purposes of administration of the study drug on the scheduled dosing interval or to allow treatment with study drug at a higher dose. Growth factors should be given according to ASCO guidelines.

If study drug cannot be administered on the scheduled day of dosing, the CBC will be repeated weekly for up to and including three weeks until the ANC is 1,200/mm^3. If these hematological criteria are met, study drug may be administered according to the dose adjustments outlined in Section 7.1.8.6.1.

If ANC remains < 1200/mm^3 or platelet count < 100,000/mm^3 three weeks after the scheduled day of dosing, the subject must be withdrawn from protocol treatment. In addition, the delay in dosing will be considered a serious adverse event and must be reported according to the adverse reaction guidelines.

All non-hematologic CTCAE v3.0 grade 2, 3 and 4 adverse events must have resolved to at least Grade 1 (excluding alopecia and lab values reflecting known liver or bone disease) prior to repeat dosing. Baseline CTCAE v3.0 Grade 2 elevations in transaminases, bilirubin and/or alkaline phosphatase must have resolved to the level defined by the inclusion criteria prior to repeat dosing.

7.1.8.6 Dose Modification Guidelines:

If multiple adverse events are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single toxicity observed. If unacceptable toxicity occurs drug is withdrawn. Upon resolution of the toxicity, subjects continue treatment at one dose level below the dose level administered. If more than a two dose level reduction is required for continued treatment of any subject, then the subject will be withdrawn from protocol treatment.

Dose Reduction Schedule-Cycle 1*

Dose Level	Dose	Regimen/Day
0	75 mg/m^2/d	qd x 2 weeks during RT
-1	60 mg/m^2/d	qd x 2 weeks during RT

*Blood counts (ANC and PLT) drawn Day 8 and Day 15. Adjust dose based on dose adjustment criteria.

Dose Reduction Schedule-Cycle 2 and beyond (if used)

Dose Level	Dose	Regimen/Day
0	200 mg/m^2/d	d1-5 q 28 d
-1	150 mg/m^2/d	d1-5 q 28 d
-2	100 mg/m^2/d	d1-5 q 28 d

Subjects who require dose reductions to a dose level of <100 mg/m^2/d of study drug will be removed from protocol treatment.

7.1.8.6.1 *Hematologic Criteria for Dose Modification:*

The dose of study drug administered for subsequent cycles will be determined according to the nadir ANC or nadir platelet count of the immediately previous cycle (see table for Dose Reduction Schedule-Cycle 2-7

If ANC <1,200 or platelet count <100,000 at any given time while on therapy, delay restarting therapy until hematological recovery (ANC ≥ 1,200 and platelet count ≥ 100,000).

If ANC <500 for seven days or ANC <500 with fever and/or platelet count <50,000, dose reduction by one dose level is recommended.

Two or more weeks of therapy delay will require dose reduction. The dose reduction recommended is the next lower dose level (e.g., 150 mg/m^2/day to 125 mg/m^2/day, etc.).

Dose Adjustment Criteria

Nadir ANC/mm^3	Nadir Platelets/mm^3	Study Drug Modification
≥1,200	≥ 100,000	Dose unchanged from previous
1,199-1000	< 100,000-75,000	Delay therapy until recovery then dose unchanged from previous
< 1000	< 75,000-50,000	Decrease dose to next lower dose level
< 500 with fever T>38.3°C or < 500 for 7 days	< 50,000	Decrease dose to next lower level

There are no dose escalations allowed.

7.1.8.6.2 *Non-hematologic Criteria for Dose Modification:*
For CTCAE v3.0 Grade 2 or less non-hematologic toxicity, no dose reductions will be required.

For Grade 3 or 4 non-hematologic toxicity (including GI toxicity unresponsive to standard therapy) delay in dosing is recommended until toxicity resolves to baseline or Grade 1. Dose reduction to the next lower dose level is also recommended (e.g., 200 mg/m^2/day to 150 mg/m^2/day, etc.). The reasons clearly explaining the specific dose reduction used must be documented and recorded in the CRF.

If no further CTCAE v3.0 Grade 3 or 4 non-hematologic toxicity occurs on subsequent repeat dosing, then the total dose to be administered for the next cycle will be the same as the dose administration during the previous cycle. That is, the patient will continue at the reduced dose. If these events recur, then the subject must be withdrawn.

All non-hematologic CTCAE v3.0 Grade 2, 3 and 4 adverse events must have resolved to at least CTCAE v3.0 Grade 1; or for baseline CTCAE v3.0 Grade 2 elevations in transaminases, bilirubin, and/or alkaline phosphatase, to the level defined by the inclusion criteria (Section 3. 1.) prior to repeat dosing.

7.1.9 Criteria for Discontinuation of Temozolomide:
Temozolomide may be discontinued for any of the following reasons:

- Undue toxicity, which in the opinion of the treating physician precludes further safe delivery of temozolomide.
- At any time when there is documented radiographic intracranial progression, as defined in Section 11.2.3; (progression of existing disease); new brain parenchymal metastases or development of leptomeningeal disease.
- The development of vertebral bony or spinal parenchymal disease will not be considered neurologic progression.
- After completion of 2 cycles of temozolomide after whole brain radiotherapy, temozolomide may be discontinued and any other chemotherapy regimen (as long as it does not include gefitinib) is permitted. At the investigator's discretion, temozolomide may be continued beyond 2 cycles, (up to a maximum of 6 post-radiation cycles) if the patient has stable CNS disease. If during this (2-month) period, systemic progression requires the use of chemotherapy, investigators are encouraged to continue temozolomide for two cycles post radiation, and use one of the regimens listed listed in Section 9.3.2. However, investigators may stop temozolomide and choose any chemotherapy they feel appropriate. In the event of progressive systemic disease during the 2- cycle post radiation temozolomide phase of the

study, phase I data supports the use of temozolomide and other chemotherapeutic agents, as described in Section 1.6.3 and defined in Section 9.3.

7.1.10 Combining Other Chemotherapy Agents with Temozolomide:
After completion of 2 cycles of temozolomide following whole brain radiotherapy; temozolomide may be continued longer, either as a single agent or in combination, as indicated in Section 9.3.

7.2 Gefitinib[113] NSC# 715055

See package insert for further information.

7.2.1 Source and Formulation
Gefitinib will be provided by CTEP/NCI. It will be supplied to the investigator as brown, film-coated tablets for use; each tablet will be of 250 mg strength (Formulation # F12653). Descriptive information for gefitinib can be found in the Investigator's Brochure (available from the NCI's Pharmaceutical Management Branch 301-496-5725). For U.S. and Canadian centers, tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each carton of trial material will have an investigational-use label permanently affixed to the outside, stating that the drug is to be used only for investigational purposes. Other names: AstraZeneca ZD1839, Iressa™

7.2.2 Storage and Stability
All investigational products must be kept in a secure place under appropriate storage conditions. For U.S. centers, all trial treatment will be stored in a lockable storage area, between 20-25°C (68-77°F), and protected from light. For Canadian centers, all trial treatment will be stored in a lockable storage area, between 15-30°C (59-86°F), and protected from light.

7.2.3 Agent Ordering
Gefitinib may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of investigational agents between institutions (unless prior approval from PMB is obtained). Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN Rm. 7149, Bethesda, MD 20892.

7.2.4 Agent Accountability
The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form. *See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs (http://ctep.cancer.gov/requisition/storage.html).*

7.2.5 Route of Administration**:** Oral. Gefitinib treatment will be taken once a day, every day about the same time. It can be taken with or without food. The effect of food on the absorption of gefitinib is not considered to be clinically relevant. If the subject forgets to take a dose, they should take the last missed dose as soon as they remember, as long as it is at least 12 hours before the next dose is due.

7.2.6 Method of Administration**:** Whenever possible, whole tablets should be administered. Gefitinib tablets cannot be crushed. Experimentation has shown that gefitinib tablets will break up into a fine dispersion within 5 to 7 minutes when they are dropped whole into lukewarm water. There are felt to be no risks to the chemical stability of gefitinib providing this process occurs immediately prior to administration by the subject. The only risk is felt to be concerned with ensuring delivery of the whole dose, as a certain amount of deposition of powder on the surfaces of the container will occur while the container is being emptied.
Iressa tablets have not been deliberately formulated to be dispersible tablets; however, in circumstances where dosing of whole tablets is not possible, such as patients being unable to swallow or being fed through nasogastric tubes, tablets may be administered as a dispersion in water. Liquids other than water should not be used, and the tablets should not be crushed or ground. Care should be taken to ensure that the whole dose is administered.

The following procedure is recommended for administering dispersed whole tablets to subjects who are unable to swallow:

Drop the required number of gefitinib tablets into an appropriate container (ideally, a clear glass to help confirm administration of all the dispersed material) containing at least 50 ml of lukewarm water. Stir the liquid continuously to ensure complete break up of the tablet(s). The tablet(s) will be broken up into a fine dispersion in approximately 6 minutes. Alternatively, the tablet(s) can be stirred occasionally, in which case the time taken for a complete dispersion is approximately 10 to 15 minutes. The dispersed tablet(s) must be administered immediately to or by the subject. Rinse the container with a small amount of water to ensure removal of any material adhering to the walls of the container and administer the additional water to the subject.

Since no data are available concerning the stability of the dispersed tablet, administration to the subject should occur immediately after dispersion is complete.

Confirmation that the subject has received the whole dose and that it was administered in this fashion should be included on the subject dispensing record.

7.2.7 Treatment

7.2.7.1 Gefitinib during Whole Brain Radiotherapy

Study drug will be administered orally, once a day, at the start of WBRT (whole brain radiotherapy) at 250 mg/day. No other chemotherapy agent will be administered during this time. Patients should avoid grapefruit juice and other citrus juices as they may interfere with the absorption of gefitinib.

7.2.7.2 Gefitinib after Whole Brain Radiotherapy

Gefitinib will be continued orally, once a day, after completion of WBRT (whole brain radiotherapy) at 250 mg/day. Treatment shall be continued until CNS progression or a maximum of 6 months; gefitinib can be discontinued for systemic progression at the investigator's discretion. The investigator is encouraged but not required to give at least 2 months gefitinib post-radiotherapy. Other chemotherapeutic agents (as long as the regimen does not include temozolomide) may be initiated at any time four weeks after completion of whole brain radiotherapy.

7.2.8 Dose Modification Guidelines

The dose of gefitinib is 250mg po qd.

The known adverse events may merit temporary or permanent discontinuation of gefitinib, at the discretion of the treating physician. Dose reductions for diarrhea should occur only when the patient has received proper antidiarrheal treatment.

Dose interruptions should be used as the first approach to managing toxicity. Repeat dose interruptions are allowed as required, for a maximum of 21 days on each occasion**.** If toxicity recurs after drug re-challenge and, if further interruptions are considered insufficient to manage the toxicity, dose reduction to 250 mg every other day may be considered.

7.2.9 Combining chemotherapy agents with gefitinib

The results of the INTACT trials 1 AND 2 demonstrate that gefitinib can be safely combined with chemotherapy agents, (i.e., gemcitabine, cisplatin, paclitaxel, and carboplatin).[114,115] Thus, the use of chemotherapy for *systemic disease* while patients are receiving gefitinib for CNS disease is permitted at the investigators discretion. See Section 9.3.

Please note, that the safety of gemcitabine + cisplatin, and paclitaxel + carboplatin have been demonstrated and thus, the combination of gefitinib with these agents is reasonable. However, the safety of gefitinib with other agents has not been as fully evaluated, such that combinations with docetaxel, vinorelbine or Alimta cannot be recommended. There are data that showed enhanced toxicity was seen with vinorelbine combined with gefitinib and the clinical trial evaluating this combination was closed early. The investigators are not aware of data supporting the dosing and safety of Alimta.

7.2.10 Reported Adverse Events and Potential Risks:

- ✓ Constitutional Symptoms: fatigue, asthenia
- ✓ Dermatology/Skin: skin rash, acne, dry skin, pruritus, nail changes
- ✓ Gastrointestinal: nausea, vomiting, diarrhea, dry mouth, stomatitis, anorexia, dehydration, mucositis
- ✓ Hepatic: increased liver transaminases
- ✓ Ocular/Visual: uveitis, corneal erosions, dry eyes, blepharitis, aberrant eyelash
- ✓ Renal: increased creatinine

- ✓ Pulmonary: pneumonitis, pulmonary infiltrates

Also reported on ZD1839 trials but with the relationship to Iressa still undetermined:

- ✓ Allergy/immunology: allergic reactions including angioedema and urticaria (rare)
- ✓ Bone/Bone Marrow: anemia, leukopenia, thrombocytopenia
- ✓ Cardiovascular (Arrhythmia): tachycardia,
- ✓ Cardiovascular (General): edema
- ✓ Constitutional Symptoms: chills, weight loss
- ✓ Dermatology/skin: alopecia, toxic epidermal necrolysis (rare), erythema multiforme (rare)
- ✓ Gastrointestinal: taste perversion, pancreatitis (rare)
- ✓ Hemorrhage: hematuria, epistaxis, CNS hemorrhage
- ✓ Hepatic: hyperbilirubinemia
- ✓ Metabolic/Laboratory: hypokalemia, increased lactic dehydrogenase, hypofibrinogenemia
- ✓ Musculoskeletal: weakness
- ✓ Neurology: depression, paraesthesia, motor neuropathy
- ✓ Ocular/Visual: photophobia, ambylopia
- ✓ Pain: headache, back pain, abdominal pain
- ✓ Renal/Genitourinary: albuminuria, urinary frequency, proteinuria
- ✓ Other: sudden death (2 cases)

Patients with worsening pulmonary symptoms of new onset or worsening dyspnea, cough, or fever should be promptly evaluated for interstitial pneumonitis and treated as clinically indicated. gefitinib should be temporarily discontinued pending diagnosis of the nature of the pulmonary disorder. Gefitinib should be permanently discontinued if a diagnosis of interstitial pneumonitis/pneumonia is confirmed and is considered to be related to gefitinib. There have been a total of 12 incidences of CNS hemorrhage reported among patients on NCI sponsored studies of gefitinib. There have been five reports of CNS hemorrhage of the 48 patients enrolled in the pediatric studies, four events, including one fatality, occurred among 33 patients enrolled on a study of concurrent gefitinib and radiation followed by continued gefitinib and one event occurred in a patient with ependymoma receiving single agent gefitinib. There have been 7 patients with CNS hemorrhages into primary or metastatic tumors reported among 1355 patients enrolled in the adult studies. Four adult patients with hemorrhage had gliomas out of a total of 290 patients enrolled in the glioma studies.

Potential Drug Interactions:

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

The use of drugs that alter gastric pH (e.g. proton pump inhibitors and H2 antagonists) may interfere with the absorption of gefitinib. As a result, these drugs should be administered at least 4 hours after gefitinib administration.

CYP 3A4 is believed to be involved in the metabolism of gefitinib. The combination of a single dose of 500 mg gefitinib with rifampicin, a potent CYP 3A4 inducer, resulted in an 83% reduction in the mean exposure (AUC). Therefore, Iressa should not be administered with agents that are inducers of the cytochrome P450 CYP3A4.

The mean exposure (AUC) of a 250 mg single dose was increased by approximately 80% in the presence of itraconazole, a potent CYP 3A4 inhibitor. Agents which inhibit CYP 3A4 can be

given with caution but are not contraindicated in patients receiving gefitinib at the current recommended doses of 250 mg and 500 mg.

7.3 Clinical Trials Agreement

The agent*(s) (hereinafter referred to as "Agent[s]") gefitinib* , used in this protocol is/are provided to the NCI under a Clinical Trials Agreement *(CTA)* between AstraZeneca *(hereinafter referred to as "Collaborator(s)")* and the NCI Division of Cancer Treatment, Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent*(s)* in this study:

Agent*(s)* may not be used outside the scope of this protocol, nor can Agent*(s)* be transferred or licensed to any party not participating in the clinical study. Collaborator*(s)* data for Agent*(s)* are confidential and proprietary to Collaborator*(s)* and should be maintained as such by the investigators.

For a clinical protocol where there is an investigational Agent used in combination with *(an)*other investigational Agent*(s)*, each the subject of different CTAs, 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 must provide all Collaborators with 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 which 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 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.

d) The NCI encourages investigators to make data from clinical trials fully available to Collaborator*(s)* for review at the appropriate time *(see #5)*. Clinical trial data developed under a CTA will be made available exclusively to Collaborator*(s)*, the NCI, and the FDA, as appropriate.

e) When a Collaborator wishes to initiate a data request, the request should first be sent 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.

f) Any data provided to Collaborator*(s)* 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.

g) Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator*(s)* for advisory review and comment prior to submission for publication. Collaborator*(s)* will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator*(s)*'s intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator*(s)* for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, Maryland 20892
FAX *(301)* 402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator*(s)*.

7.4 Criteria for Removal From Protocol Treatment

- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.

7.5 Chemotherapy Modality Review

The Medical Oncology Co-Chair, H. Ian Robins, M.D., Ph.D., 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. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **per protocol**; **variation, acceptable**; **deviation unacceptable**; **not evaluable for chemotherapy review,** or, **incomplete chemotherapy**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

7.6 Adverse Event Reporting—RTOG AE TELEPHONE LINE (215) 717-2762 or (800) 227-5463 x4189

7.6.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html All appropriate treatment areas should have access to a copy of the CTCAE v3.0. See the RTOG procedure manual for general Adverse Event Reporting Guidelines.

7.6.2 An investigational agent supplied under an NCI-sponsored IND is being used and a commercial agent is being used in this protocol. Reporting should follow the guidelines for investigational agents, therefore, all SAEs will be reported using the **Adverse Event Expedited Reporting System** (AdEERS). Reporting requirements and timing of reporting are dependent on the Phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the protocol and/or Investigator's Brochure.

7.6.3 The following table will outline the reporting requirements for this study.
Phase II/III Studies

UNEXPECTED EVENTS		**EXPECTED EVENTS**	
Grades 2 - 3 Attribution Possible, Probable, or Definite	**Grades 4 and 5 Regardless of Attribution**	**Grades 1 - 3**	**Grades 4* and 5 Regardless of Attribution**
Expedited report within 10 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to RTOG Headquarters within 24 hours of discovery. Expedited report to follow within 10 working days. Death—see 7.6.4	Adverse Event Expedited Reporting NOT required.	Report by phone to RTOG within 24 hours of discovery. Expedited report within 10 working days. *Grade 4 Myelosuppression events submitted on case report forms.
Note 1	Telephone number available 24 hours daily: (215) 717-2762 or (800) 227-5463, ext. 4189		
Note 2	Report the events using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0		
Note 3	For **Hospitalization** only – Any medical event equivalent to CTCAE Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.		
Note 4	A list of agent specific expected adverse events can be found in the protocol document and/or consent form.		
Note 5	**Reactions considered *definitely* not treatment-related should not be reported.** However, a report should be submitted if there is reasonable suspicion of drug effect.		

Known/expected adverse events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, noted in the drug insert, or in the Investigator's Brochure.

Unknown/unexpected adverse events are those thought to have resulted from the agent, e.g., temporal relationship but not previously identified as a known effect.

7.6.4 Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment must be telephoned to RTOG Headquarters Adverse Events (AE) telephone line, (215) 717-2762, or to 1-800-227-5463, X4189 within 24 hours of discovery. Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG Headquarters via the AE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 10 days.

7.6.5 Expedited reports are submitted to CTEP via the secure AdEERS application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). AEs reported through AdEERS also must be reported in routine study data submissions (appropriate case report forms). Please use the patient's case number as the patient ID when reporting via AdEERS.

7.6.6 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at http://ctep.info.nih.gov. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG

study/case numbers). This form will take the place of the FDA Form 3500 and **must be mailed within 30 days of AML/MDS diagnosis** to the following addresses:

Investigational Drug Branch	RTOG Headquarters
(NCI/CTEP)	AML/MDS Report
P.O Box 30012	1818 Market Street Suite 1600
Bethesda, MD 20824	Philadelphia, PA 19103

All forms submitted to RTOG Headquarters **must include the RTOG study and case numbers**; the non-RTOG intergroup study and case numbers must be included, when applicable.

8.0 SURGERY

Not applicable.

9.0 OTHER THERAPY

9.1 Dexamethasone

See package insert for further information.

Patients should be placed on dexamethasone at the time of brain metastasis diagnosis. The starting dose should be 4-16 mg per day of dexamethasone in divided doses, or equivalent doses of other types of glucocorticoids. Steroids will be continued without taper throughout radiation therapy. At the completion of radiation therapy, a steroid taper may be initiated at the discretion of the treating physician. In patients who cannot tolerate taper and/or cessation of steroids, the steroid dose will be maintained at the lowest dose consistent with good medical practice.

9.1.1 Chemistry: Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11, 17, 21-trihydroxy-16-methyl-pregna-1, 4-diene-3, 20-dione.

9.1.2 Toxicity: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, peptic ulcer, skin changes (thinning), convulsions, vertigo, headache, endocrine abnormalities, ophthalmic changes, and metabolic changes.

9.1.3 Formulation: Dexamethasone is available in a variety of potencies in capsule or tablet form.

9.1.4 Storage and stability: Dexamethasone is to be stored at room temperature.

9.1.5 Administration: The drug is administered orally or intravenously.

9.2 Antiemetics and analgesics

Other drugs including anti-emetics and analgesics for treatment of systemic cancer may be given at the discretion of the patient's physician and must be recorded on the RTOG data form.

Prophylactic antiemetics must be administered to all subjects prior to temozolomide administration. (Since this is an oral drug, episodes of emesis will result in under dosing.)

9.3 Other Chemotherapy

The use of other chemotherapy agents is restricted and these restrictions vary by arm:

9.3.1 Arm 1 (WBRT+SRS only):

Chemotherapy for treatment of systemic disease should be withheld during the radiation phase of protocol treatment.

No other treatment specifically for brain metastases should be given until a recurrence is detected. Chemotherapy after completion of radiation therapy will be allowed, at the Investigator's discretion while the subject is on study. There are no restrictions on the selection of chemotherapy, but these patients should not receive either temozolomide, or gefitinib, either singly or in other combinations.

9.3.2 Arm 2 (temozolomide):

At the investigators' discretion, temozolomide may be continued beyond 2 cycles to a maximum of six cycles.

Chemotherapy, other than temozolomide, for treatment of systemic disease should be withheld during the radiation phase of protocol treatment.

No other treatment specifically for brain metastases should be given until a recurrence is detected. Protocol chemotherapy after completion of radiation therapy requires at minimum, the use of 2 cycles of temozolomide, as defined in Section 7.1.8.3. After completion of 2 cycles of temozolomide after whole brain radiotherapy, temozolomide may be discontinued and any other chemotherapy regimen (as long as it does not include gefitinib) is permitted.

Phase I data (see Section 1.6) are available to support the following three regimens in combination with temozolomide:

docetaxel 80 mg/m^2 i.v. Day 1
paclitaxel 175 mg/m^2 i.v. Day 1
cisplatin 75-100 mg/m^2 i.v. Day 1

Temozolomide dose should be reduced to 150mg/m^2 when used in combination with one of the aforementioned agents.

Phase II data are also available for a small cohort of 8 patients with lung cancer treated with temozolomide plus gemcitabine-based doublets. Eight patients with NSCLC were treated every 21 days with

temozolomide:	150 mg/m^2 Days 1 to 5
+ gemcitabine:	1,000 mg/m^2 Days 1, 8
+ vinorelbine:	25 mg/m^2 Days 1, 8
OR	
temozolomide:	150 mg/m^2 Days 1 to 5
+ gemcitabine:	1,000 mg/m^2 Days 1, 8
+ cisplatin:	50 mg/m^2 Days 1, 8

Overall, the treatment was generally well tolerated, with Grade 2/3 neutropenia (n = 2), Grade 2/3 anemia (n = 3), Grade 2 neurotoxicity (n = 3) and Grade 1 nausea (n = 1). Five of 8 (62%) patients had a major response, including 3 CRs (2 patients not evaluable for response). These combinations therefore demonstrated high antitumor activity with low toxicity.

9.3.3 Arm 3 (gefitinib):

Chemotherapy for treatment of systemic disease should be withheld during the radiation phase of protocol treatment.

No other treatment specifically for brain metastases should be given until a recurrence is detected. Protocol therapy after completion of radiation therapy requires the use of gefitinib until CNS progression or a maximum of 6 months, as defined in Section 7.2.7.2. After completion of whole brain radiotherapy, any other chemotherapy regimen (as long as it does not include temozolomide) is permitted. Gefitinib should be continued unless there is clear evidence for intracranial progression.

9.4 Anticonvulsants

9.4.1 A patient who has been randomized to receive gefitinib may not be on an enzyme-inducing anti-convulsant medication (phenytoin, carbamazepine, phenobarbitol, mysoline, trileptal). If they have been started on such a drug, they should be immediately converted to a non-enzyme-inducing anti-convulsant (keppra, depakote, topamax, lamictal or neurontin) prior to the first dose ofgefitinib. Non-enzyme inducing agents include: depakote (valproic acid), keppra (levetiracetam), topamax (topiramate), lamictal (lamotrigine), and neurontin (gabapentin). Although many of these drugs have been successfully used in neuro-oncology patients, keppra is the most popular due to ease of administration. Of the non-enzyme inducing drugs, only depakote is FDA approved as a single agent anti -seizure medication.

9.4.2 If you wish to convert a patient from a preexisting enzyme inducing agent (e.g., dilantin (phenytoin), tegretol (carbamazepine), phenobarbital), you may wish to consult a neurologist. One possible example of such a conversion is provided below: initiate depakote 250mg BID x 2 days; then 250mg QD x 2 days; then check level (target 50 –100). Increase in increments of 250mg QD as necessary after first level done. When target level is reached, then taper as follows: dilantin 100mg/day; tegretol 200mg /day; phenobarbital 30 mg/day. A patient may begin therapy per protocol on the gefitinib arm, 24 hours after the last dose of the enzyme-inducing agent.

9.5 Prohibited Medications

Growth factors aimed at increasing the number of neutrophils and platelets are permitted but cannot be used to induce elevations for the purposes of administration of study drug on the scheduled dosing interval or to allow treatment with study drug at a higher dose. Growth factors should be given according to ASCO guidelines.

No other investigational drugs will be allowed during the study.

Other immunotherapy or biologic therapy (excluding growth factors) may not be used while the subject is on study.

(Use of erythropoietin is allowed on this study.)

9.6 Palliative radiation Therapy

Radiation therapy to painful bony lesions will be allowed while the subject is on study. No more than 15% of bone marrow may be irradiated. Dates of radiation, dose, field and outcome should be recorded in the CRF.

9.7 Permitted Supportive 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.

9.7.1 Anticonvulsants

9.7.2 Antiemetics

9.7.3 Anticoagulants

Patients taking warfarin or Coumadin should be monitored regularly for changes in prothrombin time or INR (blood tests of blood clotting time), and monitored at least monthly at the time gefitinib is started.

9.7.4 Antidiarrheals

9.7.5 Analgesics

9.7.6 Hematopoietic Growth Factors

9.7.7 Prophylaxis for pneumocystis carini, during the radiotherapy stage of the protocol for patients receiving temozolomide, or when the patients lymphocyte count drops below 300 is strongly recommended, e.g., double strength trimethoprim sulfamethoxazole PO BID Q Saturday and Sunday, or pentamidine 300mg IV or by inhalation Q 4 weeks.

9.8 Non-permitted Supportive Therapy

Not applicable to this study

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

								Continued Follow-up	
Assessment	Pre-Regis	Pre-SRS Wk 4	Monthly During Protocol Drug Treatment	Month 3	Month 6	Month 9	Month 12	Every 3 Months Year 2	Every 6 Months Thereafter
History	X								
BrCS, LCS, EQ-5D [a]	X[c]	X		X	X	X	X		X[a]
FACT-G[a]	X[c]			X	X		X		
Performance Status (Zubrod, NFS)	X			X	X	X	X	X	X
CBC/differential, platelets	X		X						
MRI of Head[b] and reports submitted	X			X	X	X	X	X	X
Liver Function Test	X		X						
Serum Pregnancy Test[d]	X								
Document Steroid Dose	X	X		X	X	X	X	X	X
CT Chest/Abdomen/Pelvis	X								
Bone Scan	X								

a. BrCS (brain) and LCS (lung) cancer symptom subscales and the EQ-5D to be obtained pre-registration, pre-SRS (week 4) and at months 3, 6, 9, 12, 18, and 24. The general FACT-G form to be

obtained at pre-registration and at months 3, 6, and 12. If possible, QOL should continue to be measured post-progression and at the very least, at the first timepoint post-progression.

b. Mandatory to establish number of brain metastases. Pre-study and follow up scans must be MRIs.
c. Pre-treatment obtain forms in advance of randomization.
d. Serum pregnancy test within 24 hours of randomization.

11.2 Evaluation Points

11.2.1 General evaluations and a contrast-enhanced MRI are required within 2 weeks prior to registration and every 3 months thereafter.

11.2.2 Patient examinations at the completion of radiotherapy and thereafter at each interval evaluation as specified in Section 11.1.

11.2.2.1 Patients will be seen by the radiation oncologist at least weekly, and more often if necessary, during the 3 weeks of whole brain radiation therapy.

11.2.3 Criteria for CNS Progression

11.2.3.1 Assessment: The treating radiation oncologist will measure and calculate the bi-dimensional product for each of the 1-3 brain metastases identified at baseline. The bi-dimensional product is defined as the largest dimension multiplied by the dimension perpendicular to the largest dimension. This value will be recorded on the baseline form and every subsequent follow-up form. The appearance (yes/no) of any new brain metastases will be recorded on all follow-up forms.

Baseline and follow-up MRIs (not SRS planning scan) will be used for tracking of baseline lesions and for the determination of the appearance of new lesions. A new lesion that appears on SRS planning scan will not be recorded on a follow-up form until/unless it appears on a follow-up MRI.

11.2.3.2 Definition of CNS Progression

CNS progression will be defined as any increase in perpendicular bi-dimensional tumor area for any of the 1-3 tracked brain metastases, by any amount, or the appearance of any new brain metastasis on a follow-up MRI (SRS planning scan will not be used to evaluate CNS progression).

For lesions smaller than 1 cm in maximum diameter, a maximum increase of 50% in perpendicular bi-dimensional treatment area will be necessary to score as progression. This caveat is included to account for potential variability in measurement, which will be most susceptible to proportionate errors at smaller sizes. For greater than 1 cm lesions, the definition will use a 25% rule for change.

11.2.3.3 Distinguishing Progression from Radionecrosis

All patients with reported progression should undergo further evaluation in an effort to distinguish radionecrosis from disease progression. If the distinction cannot be made, the Study Chair should be called and the imaging study submitted to RTOG HQ for Dr. Sperduto's review.

11.3 Survival

The duration of survival will be from registration until death.

11.4 Quality of Life

The Functional Assessment of Therapy-Brain (FACT-Br) has previously been shown to have high validity and reliability coefficients .[93] The FACT-Br consists of the general core instrument (FACT-G) plus the brain symptom-specific subscale. The FACT-G includes the following domains: physical well-being (PWB), 7 items; social/family well-being (SWB), 7 items; emotional well-being (EWB), 5 items; and functional well-being (FWB), 7 items. The brain symptom-specific subscale consists of 23 items. This study will also collect the 7-item Lung Cancer Subscale (LCS), which assesses symptoms commonly reported by lung cancer patients. All these items are rated on 5-point scales ranging from 0 for not at all to 4 for very much. Higher scores are representative of better patient-related health and/or fewer symptoms. FACT-L (the FACT-G core instrument plus the LCS subscale) has previously been validated in patients with lung cancer .[94] As well, the LCS-subscale has been shown to be a useful instrument in a recent randomized trial of patients with metastatic non-small cell lung cancer .[96]

The EuroQol (EQ-5D) generic health index is a frequently used simple multi-attribute health-status classification system that comprises a five-part questionnaire and a visual analogue self-rating scale. The questionnaire may be used as a health index to calculate a 'utility' value or as a health profile. The EQ-5D defines health according to five dimensions: mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. The standard five-dimension classification defines 18 different health states. The validity, reliability and responsiveness of EQ-5D haves been established [116]. EQ-5D has demonstrated moderate to high correlations with measures of impairment and high correlations with disability measures. Some patients with severe long-standing disease had health states, which attracted utility values below zero, i.e. from a societal perspective they were regarded as being in states 'worse than death'. The EQ-5D is simple to use, valid, responsive to change, and sufficiently reliable for group comparisons.

11.5 Cause of Death

A secondary objective of this study is to compare the rate of patients with neurologic death versus those with non-neurologic death. Therefore, it is important to record the cause of death according to the following definitions:

11.5.1 Neurologic death: Patients will be considered to have died neurologic deaths (coded as "Brain Metastases") if they had stable systemic disease and progressive neurologic disease consisting of expanding intracranial masses, CNS hemorrhages, hydrocephalus resulting in herniation or fulminant meningeal carcinomatosis.

11.5.2 Non-neurologic death: Any death that cannot be classified as a neurologic death, by the criteria in 11.5.1, will be considered a non-neurologic death, and coded appropriately from the choices provided on the follow-up form.

11.6 Steroid Dose

A secondary objective of this study is to compare the change from baseline in steroid dependence at six months (decrease, stable, increase) between the treatment arms. Therefore, it is important to record the steroid dosage at baseline and at each follow-up timepoint.

11.7 Criteria for Removal from Protocol Treatment

11.7.1 Unacceptable toxicity

11.7.2 The patient may terminate treatment at any time for any reason, although data collection will continue.

12.0 DATA COLLECTION

Data should be submitted to:
RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

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 (10/06/04)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** FACT General **(PF)** (Pre-treatment) FACT Subscale **(PQ)** (Pre-treatment) EQ5D **(QF)** (Pre-treatment)	Within 2 weeks of registration
Treatment Form **(TF)**	At the end of WBRT and at 3 and 6 months post WBRT for TMZ (Arm 2) and every 3 months for gefitinib (Arm 3)
Follow-up Form **(F1)**	Every 3 months for 2 years; every 6 months for 2 years; then annually; also at relapse/progression, and death
Adverse Event Form **(AE)**	As applicable for toxicity assessment reporting.
FACT General **(PF)**	At 3, 6, and 12 months
FACT Subscale **(PQ)** EQ5D **(QF)**	At 3, 6, 12, 18, and 24 months

Item	Due
Dosimetry Information Pre-treatment MRI **(MR)** and Report **(ME)** Radiotherapy Form **(T1)** Stereotactic Treatment Planning Scan **(C1)** and Report **(C3)** Dose Calculation Form **(TL)** Films (Simulation and Portal or DRRs of All Fields) **(TP)** Complete Daily Treatment Record **(T5)** Composite Isodose Distribution **(T6)** Stereotactic Radiotherapy Calculation **(RS)** Stereotactic Radiotherapy Films **(RP)** (if capability exists)	Within one week of completion of radiotherapy

12.2 MRI Documentation

The contrast-enhanced MRI done pre-radiotherapy must be submitted within one week of completion of radiotherapy. If the patient undergoes salvage craniotomy, enhanced pre- and post-operative MRIs and reports must be submitted to RTOG Headquarters.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary

Overall Survival

13.1.2 Secondary

- Time to CNS progression
- Quality-adjusted survival
- Change in FACT-Br at three months (improvement, stable, deterioration)
- Change in performance status at six months (improvement, stable, deterioration)
- Change in steroid dependence at six months (decrease, stable, increase)
- Cause of death (neurologic vs. other)

13.2 Sample Size and Power Calculation

13.2.1 Primary Endpoint

The primary endpoint of this trial is overall survival. The control arm (Arm 1) will receive whole brain radiotherapy (WBRT) followed by stereotactic radiosurgery (SRS). The two experimental arms (Arm 2 and Arm 3) will add concurrent and continuing administration of temozolomide and gefitinib, respectively, to the control treatment. Analysis of RTOG 95-08 indicated that non-small cell lung cancer patients receiving WBRT+SRS had a median survival time (MST) of 5.9 months. This trial will look for a 50% (3.0 mo.) increase in MST from 5.8 months on the control arm to 8.9 months on either of the experimental arms.

This study has been designed for each experimental arm to be compared independently to the control arm. (The comparison of the two experimental arms to each other will occur only as a secondary analysis, and only if both arms have been determined to be superior to the control arm.) East-3[117] statistical software was used to design a two-arm study with overall type I and II error rates of 0.025 (one-sided) and 0.85, respectively, to detect a 50% improvement in median survival time from 5.9 months to 8.9 months. Assuming an exponential distribution, this improvement corresponds to hazard ratio of 0.67, or equivalently, a 33% reduction in hazard (death) rates from the control to the experimental arms. Also taken into account are an expected accrual of 6 patients/month (using 4/month for the two-arm calculation), nine-month follow-up, and a total of three planned analyses (including the final analysis) with an O'Brien-Flemming boundary. The sample size was estimated at 120 patients per arm, and then expanded for three arms. Adjusting for a 5% rate of ineligibility/inevaluability results in 127 patients per arm, with **a total sample size of 381 patients**.

As in RTOG 95-08, the subset of patients with solitary metastases are of interest to examine for treatment effect. From RTOG 95-08, single brain metastases patients receiving WBRT+SRS had a MST of 6.5 months. Assuming 70% of the sample will have solitary metastases, then 84 patients per arm will be sufficient to detect a 100% improvement in median survival time from 6.5 months to 13 months (hazard ratio 0.50) with 80% power, using a one-sided significance level of 0.025.

13.2.2 Power Calculations for Secondary Endpoints

The results of the primary analysis will determine which treatment arms will be of interest to compare for the secondary endpoint analyses. A Bonferroni adjustment to the significance level will be made for multiple pairwise comparisons of a given endpoint. See Section 13.5.1 for the statistical methods that will be used to analyze each secondary endpoint.

13.2.2.1 Time to CNS Progression

Time to CNS Progression is measured from the date of randomization to documentation of progression as previously defined in the protocol (Section 11.2.3.2). The cumulative incidence model will be used to analyze this data (See Section 13.5.1), and no current sample size methodology exists for this model.

13.2.2.2 Quality-Adjusted Survival Using EQ-5D

Quality-adjusted survival (QAS) has its roots in Quality-Adjusted life Years (QALY), which was developed for health care utilization. QALY incorporate the societal-based utilities of health states into expected life years for a health condition. The QALY model is QALY(h,y)

where *h* is a health state and *y* is the years of life. A patient's health state will be determined from the EQ-5D patient questionnaire. This questionnaire produces 243 possible health states for each of which EuroQol has derived a weight. (See Section 1.8 for more details on the EQ-5D.) These weights will be used to calculate quality-adjusted survival for each patient.

$WS = \sum_{0}^{T}[V(t) \cdot Q(t)]$ where *WS* is a weighted survival function. *Q(t)* is the quality-adjusted function at time *t* and *V(t)* is the length of time from time *t* to time *t+1*. This function is distributed as a normal function and differences between the mean quality-adjusted survival of two groups can be testing using the t-test. One hundred and twenty eligible and evaluable patients in each of two groups will provide 90% power to detect an effect size ($|\mu_1-\mu_2|/\sigma$) of 0.42 using a two-group t-test with a 0.05 two-sided significance level. A Bonferroni adjustment to the significance level will be made for multiple pairwise comparisons. In addition, the correlation between the questionnaire score and the visual analogue scale (VAS) will be reported for the patient group as a whole and within arm.

13.2.2.3 Health Related Quality of Life Using the FACT Brain Subscales: Change at Three Months

Please see Section 1.8 for details about the FACT Brain subscale questionnaire. As explained in that section, a difference of 5 points will be considered a meaningful change. Change at three months, categorized as improvement, stable, or deterioration, will be summarized in a 2x3 frequency table, to compare two treatment arms. Assuming the survival rate of the standard arm (MST = 5.8 months), then 70% of patients are expected to be alive at three months. In addition, assuming 85% of patients will complete both baseline and 3-month FACT Brain subscale results in a projection of 70 expected patients per arm with FACT Brain subscale data at three months. With 70 patients per arm, a 0.05 level χ^2 test will have 80% power to distinguish between two groups when the proportions in the three categories are as follows for standard vs. experimental arm, respectively: 25% vs. 50% improvement, 55% vs. 40% stable, and 20% vs. 10% deterioration, or any distribution that corresponds to an effect size, $\Delta^2 = \Sigma(\pi_{2j}-\pi_{1j})^2/[2(\pi_{2j}-\pi_{1j})]$, of 0.0702.

13.2.2.4 <u>Change in Performance Status at Six Months</u>

Zubrod score will be collected at baseline and follow-up. For the Zubrod performance scale, death is scored as 5, therefore patients with a baseline score who have died by six months will be included in the analysis with a score of 5 at six months. Assuming that six-month performance status data will be available for 90% of patients results in a projection of 108 cases with three month performance status data, per arm. With this sample size, a 0.050 level χ^2 test will have 90% power to distinguish between the groups when the proportions in the 3 categories are characterized by an effect size, $\Delta^2 = \Sigma(\pi_{2j}-\pi_{1j})^2/[2(\pi_{2j}-\pi_{1j})]$, of 0.0586.

13.2.2.5 <u>Change in Steroid Dose at Six Months</u>

Daily steroid dose will be collected at baseline and follow-up, as one of the following: 0-4 mg, >4 to ≤ 8 mg, >8 to ≤12 mg, and >12 mg. Change from baseline at six months will be evaluated to have decreased, remained stable, or increased, based on these categories. Only patients alive at six months, and with both baseline and six-month steroid dose, will be included in this analysis.

Assuming the survival rate of the standard arm (MST = 5.8 months), then 49% of patients are expected to be alive at six months. Assuming steroid data will be available for 90% of these patients, results in a projection of 52 cases with steroid data at six months, per arm. With this sample size, 0.050 level χ^2 test will have 90% power to distinguish between the groups when the proportions in the 3 categories are characterized by an effect size, $\Delta^2 = \Sigma(\pi_{2j}-\pi_{1j})^2/[2(\pi_{2j}-\pi_{1j})]$, of 0.1217.

13.2.2.6 <u>Cause of Death</u>

See Section 11.5 for the definition of neurologic death. For the comparison of cause of death (neurologic vs. other), a two group χ^2 test with a 0.05 two-sided significance level will have 89% power to detect the difference between a proportion of 0.50 and a proportion of 0.30, or equivalently, of 0.70, when the sample size in each group is 120. With a base rate other than 0.50, this test will have increased power to detect a difference of the same magnitude.

13.3 Patient Accrual

This study is projected to accrue six cases per month based on accrual rates to RTOG 95-08. Allowing low accrual during the first six months while institutions are obtaining IRB approval and becoming credentialed (when necessary), patient accrual should be completed within 70 months. If the expected rate of 6 patients per month is not reached within 18 months of study activation, then the study will be re-evaluated with respect to feasibility.

13.4 Randomization

13.4.1 Patients will be randomized using a permuted block design within strata to balance for patient factors other than institution, as described by Zelen[118]. The stratifying variables are RTOG RPA class[124] *(Class I, Class II)*, number of brain metastases *(single, 2-3)*, and the extent of extra cranial metastases *(none, present)*. Because patients with extra cranial metastases are classified as RPA class II, the combination of the three aforementioned stratifying variables will result in six, rather than eight, distinct stratification cells.

13.4.2 RPA Class I is defined as patients with: Zubrod 0-1 (KPS ≥ 70), age < 65 years, no extra-cranial malignancies, and controlled primary. RPA Class II is defined as patients with Zubrod 0-1 (KPS ≥ 70) and who do not fall into RPA Class I; in other words, patients with Zubrod 0-1and any of the following: age ≥ 65; extra-cranial metastases; or uncontrolled primary malignancy. Note: Since all patients are required to have Zubrod 0-1 and controlled primary to enter the study, these factors are not listed in the stratification definitions on the schema page.

13.5 Analyses Plans

13.5.1 Statistical Methods

Overall survival is measured from date of randomization and will be estimated by the Kaplan-Meier method --"failure" is defined as death by any cause, and all cases without a recorded death are considered censored.[119] The log-rank test will be used to compare survival between two treatment arms.[120] Time to CNS progression is measured from the date of randomization to documentation of progression as previously defined in the protocol (Section 11.2.3.2). The cumulative incidence method will be used to estimate CNS progression rates, and the time to CNS progression will be compared between two arms using the method developed by Gray.[121122] A multivariate survival analysis will be performed using the Cox proportional hazards model, in order to adjust for RPA class. Cause of death (see Section 11.5 for definition), change in the performance status at six months, change in steroid use at six months, and change in the FACT Brain subscale at three months will each be compared between two treatment arms using a two- group χ^2 test. Cause of death (neurologic vs. other) will be summarized in a 2x2 frequency table, while change in performance status, change in steroid use, and change in the FACT Brain subscale will result in 2x3 tables. Quality-adjusted survival will be compared between two treatment arms using a two-group t-test.

13.5.2 Interim Analyses of Accrual and Toxicity

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results have been submitted. In general, the interim reports will contain the following information:

a) patient accrual rate with projected completion date for the accrual phase;
b) distribution of patients with respect to pretreatment characteristics, including participation rates of women and minorities;
c) compliance rate of treatment delivery with respect to the protocol prescription;
d) the frequency and severity of adverse events.

13.5.3 Interim Analyses of Study Endpoints

Interim analyses were planned using East software, and the nominal p-values were truncated at 0.001.

There will be a first interim analysis of the primary study endpoint (survival) when there has been 74 events (deaths) combined pairwise for the standard arm and each experimental arm (i.e., Arm 1 + Arm 2 = 74 events, Arm 1 + Arm 3 = 74 events). Based on the expected accrual rate (Section 13.3), the first analysis is estimated to take place at approximately 18 months from the start of accrual. Each experimental arm will be compared to the control arm using a one-sided log-rank test with a significance level of 0.001. There will be a second interim analysis when there has been 148 events (deaths) combined pairwise for the standard arm and each experimental arm (i.e., Arm 1 + Arm 2 = 148 events, Arm 1 + Arm 3 = 148 events), which is estimated to take place at approximately three years from study activation. Each experimental arm will be compared to the control arm using a one-sided log-rank test with a significance level of 0.006. At each planned interim analysis, the p-value from the above-

mentioned analysis, and the conditional power [123] for detecting the alternative hypothesis (for each of the experimental arms) given the observed data, will be reported to the RTOG Data Monitoring Committee (DMC) in a blinded fashion. The responsible statistician may recommend early reporting of the results and/or stopping study accrual on one of the experimental arms if the treatment effect, with respect to overall survival, is highly significant, i.e. below the significance level specified previously, or if the conditional power is less than 15%. Before making such a recommendation, the other treatment arm, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study will also be taken into consideration. The DMC will then make a recommendation about the trial to the group chair.

13.5.4 Analysis for Reporting Initial Treatment Results

13.5.4.1 Primary Endpoint

This analysis will be undertaken when all patients have been potentially followed for a minimum of nine months. Only ineligible patients will be excluded from the endpoint analyses. (Ineligible patients that receive RT will be analyzed for toxicity.) This analysis will include all components of the six-month interim reports (Section 13.5.1) along with the initial treatment results. Overall survival of the experimental arms (Arm 2 and Arm 3) will each be individually compared to the control arm (Arm 1) using a one-sided log-rank test with a significance level of 0.023 (0.025 adjusted for interim analyses;). The two experimental arms (Arm 2 and Arm 3) will be compared to each other only in the case in which both arms are found to be superior to the control arm, according to the analysis plan above. RPA class will be included in a multivariate Cox model along with treatment arm to test the relative importance of these factors for survival.

Additional subgroup analyses will be performed if there are sufficient numbers of patients for the purpose of identifying patterns of treatment responses. As specified in Section 13.2, a comparison of overall survival within the subgroup of patients with solitary metastases will be performed.

13.5.4.2 Secondary Endpoints

Statistical methods for analysis of secondary endpoints are described in Section 13.5.1. The results of the primary analysis will determine which treatment arms will be of interest to compare for the secondary endpoint analyses. Pairwise comparisons of the secondary endpoints will be carried out using a one-sided significance level of 0.05. A Bonferroni adjustment to the significance level will be made for multiple pairwise comparisons of a given endpoint.

13.6 CDUS Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.7 Inclusion of Women and Minorities

In conformance with the National Institute of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we note that the recursive partitioning analysis of the RTOG database for patients entered into brain metastases trials failed to show race or gender interaction with treatment.[118] Since there are no publications found to suggest such an interaction, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races, as accrual across classes of race and gender permits.

The projected gender and minority accruals appear below:

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	7	8	15
Not Hispanic or Latino	172	194	366
Ethnic Category: Total	179	202	**381**
Racial Category			
American Indian or Alaskan Native	2	2	4
Asian	2	2	4
Black or African American	20	22	42
Native Hawaiian or other Pacific Islander	0	0	0
White	155	176	331
Racial Category: Total	179	202	**381**

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APPENDIX I

RTOG 0320

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE III TRIAL COMPARING WHOLE BRAIN RADIATION AND STEREOTACTIC RADIOSURGERY ALONE VERSUS WITH TEMOZOLOMIDE OR GEFITINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND 1-3 BRAIN METASTASES

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have non-small lung cancer that has spread to the brain (brain metastases).

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to compare the results of three different treatments for brain metastases and overall survival. Study doctors will compare the effects (good and bad) of the standard treatment (whole brain radiation therapy and stereotactic radiosurgery), the standard treatment plus the drug, temozolomide, or the standard treatment plus the drug, gefitinib on you and your brain metastases to see which is the best treatment.

This research is being done because we do not know which of these three treatments is best.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 381 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer puts you into one of the groups. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in any one of the following three groups:

1. Whole brain radiation and radiosurgery
2. Whole brain radiation and radiosurgery plus temozolomide
3. Whole brain radiation and radiosurgery plus gefitinib

Definitions:

Whole brain radiation:	The brain is treated with small amounts of radiation daily (Monday through Friday) for three weeks.
Radiosurgery:	This is a one-day, out-patient procedure during which a high dose of radiation is delivered to a small spot in the brain (your tumor) while excluding the surrounding normal brain.
Temozolomide:	This is a drug you will take daily during radiation then for 5 consecutive days out of every 28 days for 6 months after radiation.
Gefitinib:	This is a drug you will take daily during radiation and for 6 months after radiation.

If you take part in this study, you will have the following tests and procedures:

Procedure	Schedule
History, Physical and Neurological Exam	Prior to study entry, before each cycle of drug, before radiation starts, at month 3, 6, 9, 12, and every 3 months in year 2 and every 6 months thereafter.
Blood Counts, Chemistries	Prior to study entry, monthly during drug treatment,
Pregnancy test (if applicable)	Prior to study entry
Chest, Abdomen, Pelvic CT scan	Prior to study entry
Bone Scan	Prior to study entry
Brain MRI with contrast	Prior to study entry, at month 3, 9, 12, every 3 months in year 2, and every 6 months thereafter
Quality of Life Questionnaires	Prior to study entry, at week 4, month 3, month 6, month 9, month 12, month 18, and month 24

If you take warfarin or Coumadin, you will be monitored regularly for changes in prothrombin time or INR (blood tests of blood clotting time) and monitored more frequently at the time gefitinib is started.

Because you are in this study, you will have more frequent MRIs and blood tests than you would with the standard care.

In addition, you will be asked to fill out quality of life questionnaires, which take about 10-15 minutes to complete.

This study will be done as an outpatient. That means you will live at home and only need to come to the hospital for the radiation treatments. You do not need to stay overnight in a hospital. You will be seen by the radiation oncologist at least weekly and more often, if necessary, during the three weeks of whole brain radiation therapy.

The following drugs are being tested in this study**:**

Temozolomide

Gefitinib is FDA approved for the 3rd line treatment (the most effective treatment after the first two treatments have failed) of NSCLC (Non-Small Cell Lung Cancer)

Both drugs have been used in patients with brain metastases and preliminary evidence suggests they may be of benefit.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the treatment phase of the study for 6 to 12 months, but you will be followed for the rest of your life.

The study doctor may decide to take you off this study if your doctors feel it would be in your medical best interest.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is completed, but in some cases side effects can be serious or long-lasting or permanent. There also is a risk of death.

Risks and side effects related to the treatments we are studying include:

Risks Associated with Whole Brain Radiation Therapy:
(Both temozolomide and gefitinib could make the radiation side effects worse.)

Likely

- Scalp redness or soreness
- Hair loss
- Dry mouth or altered taste
- Fatigue, sleepiness
- Muffled hearing (temporary)

Less Likely

- Fever, chills, heavy sweating
- Upset stomach, nausea and/or vomiting
- Loss of appetite, taste changes
- Thrombophlebitis (blood clots)
- Headaches, seizure, weakness

Rare, But Serious

- Permanent hair loss
- Hearing loss
- Eye injury resulting in blindness
- Mental slowness, behavioral changes
- Severe damage to normal brain tissue that may require additional surgery

Risks of Radiosurgery:

Likely

- Pin site soreness for a day or two

Less Likely

- Brain swelling, which may cause any prior or existing neurologic symptoms to get worse
- Muffled hearing (temporary)

Rare, But Serious

- Radiation necrosis, which can cause brain swelling months later

Risks Associated with Temozolomide:

Likely

- Nausea and/or Vomiting
- Decrease in blood counts that may cause infection and bleeding
- Constipation

Less Likely

- Loss of appetite
- Diarrhea
- Fever
- Weight loss and/or a decrease in appetite
- Weakness
- Sores in your mouth
- Hair loss
- Numbness or tingling
- Abdominal pain/jaw pain
- Skin rash
- Weakness of hands and feet

- A temporary elevation in the blood tests that show how your liver is functioning
- Dizziness
- Swelling of the feet has been experienced by patients taking temozolomide, but this might be related to their disease or other medications.
- Drowsiness/Fatigue

Rare, But Serious

- Decreased ability to carry out daily activities
- Pneumonia
- Headache
- Difficulty with balance

Risks Associated with Gefitinib

Likely

- Skin rash like pimples, sometimes with redness face, upper arms, or chest and can be severe. The rash usually goes away once the drug is stopped, but it often disappears or reduces in severity even when the drug is being continued.
- Diarrhea (occurs in up to half of all patients) and can be severe. The diarrhea usually can be controlled with a drug called loperamide.
- Tiredness
- Weakness
- Dry skin
- Itching
- Acne
- Dry mouth
- Inflammation of the eye
- Problems with your eyelashes
- Changes in your fingernails or toenails

Less Likely

- Nausea and vomiting occasional to rare; anti-nausea medications can be given for this.
- Change in taste
- Decreased ability to digest milk and/or milk products
- Decreased appetite
- Stomach pain
- Inflammation of the lining of the mouth
- Inflammation of the lining of the digestive tract
- Dry eyes
- Bleeding from the nose
- Hair loss
- Chills
- Weakness

- Dehydration
- Swelling due to fluid accumulation in tissues
- Change in sensation, such as tingling or burning
- Light sensitivity; routine sun protection recommended
- Headache
- Sleepiness
- Depression
- Back pain
- Urinary frequency
- Blood in the urine
- Rapid heartbeat
- Decreased red cell (red cells carry oxygen to tissues) or white blood cell (white cells fight infection) levels
- Decreased potassium (which is necessary for proper body physiology) in the blood
- Abnormal kidney function test results that may indicate problems with your kidney
- Abnormal liver function test results that may indicate problems with your liver
- Abnormalities in the way the liver works have been measured, but these changes have not resulted in liver damage.
- Temporary changes on the surface of the eye have been seen in four people, which did not affect their sight. They had symptoms such as eye discomfort, itching, or slight pain. When they stopped taking gefitinib, their eyes returned to normal.

Rare, But Serious

In some patients taking gefitinib and oral blood thinners (warfarin or Coumadin), blood tests [International Normalized Ratio (INR)], which measure the ability or time for blood to clot and/or bleeding events, have been reported abnormally elevated. The elevation of INR was associated with bleeding.

- Gefitinib has caused small changes in the electrical activity of the heart in a few animals, but this has not occurred in people.
- Some patients (less than 1%) taking gefitinib get a type of inflammation of the lungs called ‘interstitial lung disorder’ or ‘interstitial pneumonia’. This type of lung disease causes worsening of existing lung problems or causes new lung problems, such as sudden onset of shortness of breath, fever, cough, and/or problems with oxygen getting through the lungs to the blood. In some patients, this lung disease has been fatal. If you should have lung problems such as shortness of breath, cough, and/or fever, you should contact your doctor immediately. Gefitinib will be stopped until your doctor has identified the cause of these lung problems. If the lung problems are related to gefitinib, it will not be restarted.

Serious side effects of gefitinib are infrequent. They are usually not severe enough to require discontinuing treatment.

You should avoid grapefruit juice and other citrus juices as they may interfere with the absorption of gefitinib.

Risks of antibiotic treatments to prevent pneumocystis pneumonia

Because there is a risk of contracting a type of pneumonia called pneumocystis pneumonia when you are receiving temozolomide at the same time as radiation therapy to the brain, you will receive one of two preventive treatments: trimethoprim-sulfamethoxazole or pentamidine. The risks are as follows:

Risks of oral trimethoprim-sulfamethoxazole:

Likely
- Nausea
- Loss of appetite
- Vomiting
- Skin rash

Less Likely
- Low white blood cell counts
- Low blood platelet counts (problems with blood clotting)
- Liver irritation resembling hepatitis
- Low red cell counts,
- Abnormalities in blood tests that measure liver functions

Rare, But Serious
- Stevens-Johnson syndrome (a severe skin reaction similar to a bad burn that can involve the lining of the mouth and eye)
- Very low white cell counts, platelet counts, red cell counts
- Allergic reaction similar to severe asthma with difficulty breathing
- Life threatening injury to the liver or kidneys

Risks of pentamidine:

Likely
- Nausea
- Loss of appetite
- Bronchospasm (difficulty breathing due to squeezing closed breathing passages in the lungs)
- Cough
- Shortness of breath
- Dizziness
- Rash

Less Likely
- Headache

Rare, But Serious
- Abnormal heart rhythms

- Low white blood cell counts
- Low blood sugar
- High blood sugar
- Pancreatitis (inflammation of the pancreas causing belly pain)
- Kidney damage
- Liver irritation resembling hepatitis
- Eye irritation
- Blurred vision

Reproductive Risks

This study may be harmful to a nursing infant or an unborn child. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while you are on this study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child. If you are unwilling to use adequate birth control measures to prevent pregnancy of a partner, you should not participate in this study. If you suspect you have caused anyone to become pregnant while you are on this study, you must tell your doctor immediately.

You cannot enroll in this study if you are pregnant. You should not nurse your baby while on this study. Women of childbearing potential and their sexual partners should use birth control throughout participation in this study. Sexual partners of study participants must use adequate birth control measures to prevent pregnancy of a partner.

Ask your doctor about counseling and more information about preventing pregnancy.

Risks associated with drawing blood from your arm

- Pain
- Bruising
- Lightheadedness,
- Infection (on rare occasions).

There may be other risks or side effects that are unknown at this time.

Risks associated with Quality of Life Study

- Time to fill out the forms (about 15 minutes)
- Possibly upsetting the patient

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with lung cancer and brain metastases in the future.

We do not know for sure that adding temozolomide or gefitinib to radiation and radiosurgery will help patients with brain metastases. That is why we are doing the study.

The possible benefits of taking part in the study are the same as receiving these same treatments without being in the study.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: *(1)* radiation therapy; *(2)* chemotherapy; *(3)* surgery; or *(4)* no treatment except medications to make you feel better.
These treatments could be given either alone or in combination with each other.
You can receive this treatment without participating in the study.
Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG).* Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration *(FDA),* the National Cancer Institute *(NCI)* or its authorized representatives, CTSU, CIRB, qualified representatives of AstraZeneca and Schering-Plough Pharmaceutical Companies, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

If you are assigned to the temozolomide or gefitinib groups, those drugs will be provided to you free of charge. The Division of Cancer Treatment, and Diagnosis, NCI, will provide you with gefitinib free of charge for this study. Every effort will be made to ensure adequate supplies of gefitinib, free of charge, for all participants. If the drug becomes commercially available for the treatment of non-small cell lung cancer in combination with brain radiation, there is a remote possibility that you may be asked to purchase subsequent supplies, your physician will discuss this with you should this situation arise.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not affect your care.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

_____	_____
Name	Telephone Number

For information about this study, you may contact:

_____	_____
Name	Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)

_____	_____
Name	Telephone Number

You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for comprehensive clinical trials information at **www.cancer.gov/clinicaltrials**
or
for accurate cancer information including PDQ (Physician Data Query) visit
www.cancer.gov/cancerinfo/pdq

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_____	_____	_____
Patient's Name	Signature	Date
_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

APPENDIX III

NEUROLOGIC FUNCTION (NF) STATUS

N F	Definition
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

APPENDIX IV
RTOG 0320

A PHASE III TRIAL COMPARING WHOLE BRAIN RADIATION AND STEREOTACTIC RADIOSURGERY ALONE VERSUS WITH TEMOZOLOMIDE OR GEFITINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND 1-3 BRAIN METASTASES

TEMODAR™ SHIPMENT FORM

Temodar™ will be shipped only to institutions that have identified a single individual for receipt of shipment. Each institution must submit this form to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration if it is the institution's first case *(the shipment form is only submitted once.)* Allow adequate processing time *(7-10 days)* before calling to register the first case.

SHIP TO:

Name: _____

Address: _____
(No P.O. Box Numbers)

_____

_____

_____

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

Group Affiliation:_____

IRB Approval Date: _____
(attach copies of IRB approval and sample consent form)

Investigator *(PI)* Signature _____ Date:_____

Investigator Name *(Print)* _____

Investigator NCI # *(Required)* _____

Return to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206

RTOG Headquarters Approval _____ Date: _____

APPENDIX V

STEREOTACTIC RADIOTHERAPY QA GUIDELINES

Below is the direct link to the RTOG Stereotactic Radiotherapy Quality Assurance Guidelines in pdf:

http://www.rtog.org/pdf_document/quality_guideline.pdf

APPENDIX VI

STEREOTACTIC FACILITY QUESTIONNAIRE

This questionnaire, with the requested supporting physics dosimetry information must be submitted for approval before any patients can be placed on RTOG Stereotactic Radiotherapy protocols. These data will help assure the RTOG quality assurance office that each institution has committed proper facilities and effort to this modality. These data will also be used by the RTOG quality assurance office in their review of protocol treatment and verification. Please include additional descriptions when necessary.

I. **General Information**

Institution Name _____RTOG Inst. #*(required)*_____

Responsible Radiation Oncologist*(s)*_____Telephone #_____

Responsible Medical Physicist*(s)*_____Telephone #_____

Responsible Research Associate*(s)*_____Telephone #_____

II. **Stereotactic Equipment:**

A. *Radiation Unit*

Manufacturer, Make & Model_____

Nominal Beam Energy _____Nominal Accelerating Potential:_____

Nominal SSD/SAD_____

Describe method to determine the variation of isocenter over range of gantry and couch angles employed. Report the results of this determination._____

_____

_____

_____

B. *Treatment Fixation System (i.e., patient's head frame relative to treatment couch (isocenter).*

Describe commercial system *(Attach vendor descriptive literature)*:_____

_____

_____

_____

Describe "homemade" system _____

_____

_____

_____

C. *Relocatable Stereotactic Head Frame or Other Immobilization/Localization System*

1. Vendor:_____

_____

2. If specially designed, please describe:_____

_____

3. Attach diagram showing dimensions of outer CT/MR fiducials.

D. *Treatment Planning System*

1. Vendor/Model:_____

If system is specially designed, please describe_____

_____

_____

2. State the ability of the system to outline the target and calculate the target volume:_____

_____

_____

3. State the ability of the system to calculate the required dose-volume data:_____

_____

_____

4. State the ability of the system to provide isodose lines superimposed on CT/MR images:_____

_____

_____

E. *Other*

Please describe any additional devices or techniques used for the stereotactic radiotherapy procedures.

_____

_____

III. **Dosimetric Parameters for Stereotactic Radiotherapy**

Note: These data should be based on procedures and data in the AAPM Calibration Protocol *(Med Phy 10:741-771, (1983))* for basic machine calibration, and upon ICRU Report #24 for depth dose distributions.

PLEASE ATTACH THE FOLLOWING INFORMATION:

A. Statement of Unit Calibration.

B. Relative Dosimetric Parameters:

1. Applicator output: cGy/MU or output relative to calibration, for all cones. Describe measurement geometry *(i.e., SSD and depth).*

2. Central axis depth dose information: table of TPR's, TMR's or percent depth dose for largest, smallest, and intermediate cone/collimator sizes.
3. Tabulated widths of the 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, and 10% isodose or dose decrement lines on three orthogonal axes through isocenter, for largest, smallest, and intermediate cone/collimator sizes. State the measurement geometry and technique used to determine these data *(as examples: "diode scans for static field at 8cm depth," or "film dosimetry in 16cm diameter phantom for (specific) multiple arc technique").*

IV. Additional Information

The following are important clinical considerations for which there are no standard dosimetry procedures. Other institutions may benefit from this information.

A. Techniques for stereotactic verification of isocenter *(couch, gantry, and collimation)* and alignment of the head frame:_____

_____

_____

B. Techniques used to verify the treatment dose via phantom measurements:_____

_____

_____

C. Any other technical descriptions unique to your system:_____

_____

_____

V. Required Before You Can Enter Cases on RTOG Stereotactic Radiotherapy Protocols

Complete this form in its entirety. Review by the RTOG Physics team may take several weeks longer if the application is incomplete.

Send this form and required documentation to
Dosimetry
RTOG Headquarters
1818 Market Street
Suite 1600
Philadelphia, PA 19103

APPENDIX VII

Drugs that Interfere with Gefitinib Metabolism, i.e., affecting CYP3A4

Inducers CYP3A4	
Carbamazepine Dexamethasone (lowest dose possible) Ethosuximide Glucocorticoids (lowest dose possible) Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St. John's wort Sulfadimidine Sulfinpyrazone Troglitazone
Inhibitors CYP3A4	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole	*Ketoconazole* Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

APPENDIX VIII

Enzyme vs. Non-enzyme Inducing Anti-Seizure Medications

EIAEDs:

Carbamazipine	(Tegretol, Tegretol XR, Carbatrol)
Oxcarbazepine	(Trileptal)
Phenytoin	(Dilantin, Phenytek)
Fosphenytoin	(Cerebyx)
Phenobarbital	
Primidone	(Mysoline)

Non-EIAEDs:

Valproic acid	(Depakote, Depakene) (Note: try to avoid inhibitor of CYP3A4)
Gabapentin	(Neurontin)
Lamotrigine	(Lamictil)
Topriamate	(Topamax)
Tiagabine	(Gabatril)
Zonisamide	(Zonegran)
Levatriacetam	(Keppra)
Clonazepam	(Klonopin)
Clonozam	(Frisium)