RADIATION THERAPY ONCOLOGY GROUP

RTOG 0320

A PHASE III TRIAL COMPARING WHOLE BRAIN RADIATION AND STEREOTACTIC RADIOSURGERY ALONE VERSUS WITH TEMOZOLOMIDE OR ERLOTINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND 1-3 BRAIN METASTASES (5/3/05)

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SCHEMA (5/3/05)(5/8/07)

S      R
T 1. Class I: < 65 years and no extra-cranial metastases
2. Class II: ≥ 65 years or extra-cranial metastases
R A
N D

A Number of Metastases
T 1. One
2. Two or three
I O
M Arm 1: WBRT + SRS
Arm 2: WBRT + SRS + temozolomide
Arm 3: WBRT + SRS + Erlotinib

Y F Extent of Extracranial Disease
Z I
E

*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. After WBRT, temozolomide may be discontinued at investigator’s discretion or continued. If continued, 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 CNS) or for a maximum of 6 additional cycles or until the drug is discontinued at the investigator’s discretion.

Arm 3: WBRT + SRS + Erlotinib 150mg/day daily beginning on day 1 of WBRT. After WBRT, the erlotinib may be discontinued at investigator’s discretion or continued. If continued, it will continue for 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 subtotal 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
1. Is there histologic proof of non-small cell lung cancer?  
2. Has a contrast enhanced, diagnostic brain MRI been done within 2 weeks prior to registration? 
3. Does the imaging demonstrate the presence of one to three intraparenchymal brain metastases? 
4. Is the maximum tumor diameter ≤ 4.0 cm? 
5. If multiple lesions are present and one is at the maximum diameter, do any of the others exceed 3.0 cm in diameter? 
6. Has patient undergone sub total resection? If yes, does residual disease measure ≤ 4.0 cm in maximum diameter? 
7. Has the patient had any previous cranial radiation? 
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? 
9. Is the patient 18 years or older? 
10. Is the Zubrod Performance Status 0-1? 
11. Is the Neurologic Function Status 0, 1, or 2 (per Appendix III)? 
12. Have required prestudy evaluations been obtained and do the laboratory values meet the criteria in Section 3.1.9? 
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.) 
14. Any evidence of leptomeningeal metastases? 
15. Are there any metastases to the brain stem, midbrain, pons, or medulla, within 10 mm of the optic apparatus? 
16. Are there known or pre-existing liver metastases? 
17. Is patient pregnant or nursing? 
18. Is patient known to be HIV positive? 
19. Any evidence of clinically active interstitial lung disease? 
20. Will patient be treated with concomitant St. John’s Wort?

(continued on next page)
RTOG Institution #

RTOG 0320

ELIGIBILITY CHECKLIST (10/06/04)(5/3/05) (4/6/06)

Case #

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

______ (N) 22. Does the patient have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib and temozolomide?

______ (N) 23. Has the patient had previous temozolomide or erlotinib?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

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

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)

(continued on next page)
The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________  Date ___________________________
1.0 BACKGROUND

1.1 Hypothesis (5/3/05)
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 erlotinib will result in better survival than WBRT + SRS alone.

1.2 Epidemiology
Metastases to the brain are the most common malignancy affecting the brain. 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%. 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.

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. Untreated patients have a median survival time (MST) of less than 7 weeks. Three prospective randomized trials involving more than 1800 patients conducted by the Radiation Therapy Oncology Group (RTOG) evaluated 9 different radiation doses and schedules. 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. 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. 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. 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. 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. 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). 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. Vecht et al. randomized 63 patients to the same regimen with similar results. 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. 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). 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. Smalley and colleagues demonstrated a statistically significant benefit in survival and fewer recurrences in 85 patients who received WBRT following surgery. 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. On the other hand, Hagan et al. found no advantage to WBRT following surgery in patients with melanoma, a radioresistant tumor. Likewise, Dorsoretz et al. found no survival advantage to low dose WBRT among 33 patients with resected solitary lesions and no active systemic cancer.

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. Over a decade of reports have suggested a role for stereotactic radiosurgery (SRS) in the treatment of metastatic brain tumors. The development of linear accelerators modified to deliver focused irradiation has expanded the availability of SRS. 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. SRS allows delivery of a high dose of focal irradiation in a single fraction to the tumor from multiple angles. 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. 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.

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. Local control to complete radiographic obliteration has been achieved in 80% to 90% of cases. Noordijk et al. treated 52 brain metastases in 33 patients with SRS. 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. 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.

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 ≤ 2.0cm, 2.1-3.0cm and 3.1-4.0cm in maximum diameter were 24Gy, 18Gy and 15Gy, respectively.
Sanghavi et al 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. 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). 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. 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 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.
There is one other trial where this population has been studied with similar results (Mangiameli).68

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) 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. 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)

<table>
<thead>
<tr>
<th></th>
<th>WBRT + TMZ</th>
<th>WBRT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo RR</td>
<td>53%</td>
<td>33%</td>
<td>.02</td>
</tr>
<tr>
<td>3 mo steroid independence</td>
<td>85%</td>
<td>49%</td>
<td>.002</td>
</tr>
<tr>
<td>CNS death</td>
<td>13%</td>
<td>28%</td>
<td>.034</td>
</tr>
<tr>
<td>Median TTP</td>
<td>7.5 mo</td>
<td>6 mo</td>
<td>.011</td>
</tr>
<tr>
<td>Median Survival</td>
<td>7.9 mo</td>
<td>4.3 mo</td>
<td>.06</td>
</tr>
</tbody>
</table>

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.

**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:


Antonadou D, et al (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/m²/d x 6 wk with concurrent thoracic XRT to 60 Gy, then 200 mg/m² 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;
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.

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

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.

1.6.5 Erlotinib (5/3/05)

Epidermal Growth Factor Receptor (EGFR)
The EGFR is a 170-kd membrane-spanning glycoprotein composed of an extracellular ligand-binding domain, a lipophilic transmembrane domain, and an intracellular tyrosine kinase (TK) domain. After ligand binding, receptor dimerization leads to TK activation and the recruitment and phosphorylation of intracellular substrates, resulting in cell proliferation, motility, adhesion, invasion, survival, and angiogenesis. Downstream signaling induced by phosphorylation of the EGFR TK complex includes activation of Ras, Raf, and mitogen-activated protein kinase (MAPK) proliferative pathway, and the signaling for apoptosis through the phosphatidylinositol 3-kinase/Akt pathway. Additionally, the signal transducers and activators of transcription (STAT) factors seem to be closely linked to the EGFR signaling pathway, thereby linking cell-surface signaling with regulation of gene expression. Activation of the EGFR autocrine pathway in cancer cells can be attributable to multiple mechanisms, including over expression of the EGFR, increased concentration of ligand, including TGF-α, decreased receptor turnover and the presence of aberrant receptors, such as the EGFRvIII, which is a truncated EGFR that has a constitutively activated TK domain that stimulates cell proliferation in the absence of ligand binding. The EGFR is over expressed in many solid tumors, including non-small cell lung cancer (NSCLC), and multiple studies have suggested a shortened survival in NSCLC patients whose tumor over expresses EGFR.

A large body of preclinical and clinical experience supports the rationale that the EGFR represents a relevant target for cancer therapy. Pharmacologic blockade of EGFR has consisted of two mechanisms: monoclonal antibodies directed at the external domain to block ligand binding and receptor activation and small molecule TK inhibitors (TKI) that compete with the ATP-binding site of the catalytic domain of the EGFR TK. Preclinically, both methods of interference have disrupted cell cycle progression by inducing G1 arrest through an increase in the protein levels of the p27kip1 inhibitor of cyclin-dependent kinases, significantly inhibited the growth of carcinoma xenografts in vivo, induced endothelial cell apoptosis and tumor cell regression, and resulted in at least additive tumor growth inhibition when combined with cytotoxic agents or irradiation without exacerbating toxicity.
Erlotinib

Erlotinib (OSI-774, Tarceva™, OSI Pharmaceuticals, River Edge, NJ; [6,7-bis(2-methoxyethoxy)-quinalizin-4-y]-[3-ethylphenyl]amine) is an orally administered, reversible, small molecule inhibitor of EGFR TKI that inhibits EGFR autophosphorylation by binding competitively to the ATP binding site of the intracellular TK domain.

Erlotinib has been evaluated in two Phase I dose escalation studies in patients with advanced malignancies.97,98 Forty patients received erlotinib in doses of 25–200 mg in three study segments in which the schedule of administration was increasingly prolonged.98 The maximum tolerated dose was 150 mg/day in the uninterrupted daily administration schedule, with dose limiting toxicities consisting of watery diarrhea and acneiform rash. The diarrhea was mild in most cases and managed successfully with aggressive use of loperamide. Severe diarrhea (grade 3 or 4) occurred in only two patients and was not noted after the protocol was amended to include scheduled loperamide use.98 Development of the acneiform rash was dose dependent and precluded dose escalation above the recommended phase II dose of 150 mg/day. The steady state concentration at 150 mg/day exceeded the concentration deemed necessary for antitumor effects based on preclinical models. Pharmacodynamic assessment of the cellular impact of erlotinib in the skin, using pre- and post-treatment skin biopsies, detected a statistically significant decrease in the ratio of activated EGFR (64% pre-treatment vs. 49% post-treatment, p=0.02), as well as a significant increase in the average number of epidermal cells with nuclear staining for p27 (p=0.004).99 One patient with sequential pre- and post-treatment tumor biopsies demonstrated decreased staining for phosphorylated EGFR and complete abolition of activated Akt. A second patient with paired tumor biopsies revealed reduced phosphorylated Erk staining.99 One patient with metastatic renal cell carcinoma attained an objective antitumor response, while minor responses or prolonged stable disease were seen in heavily pretreated patients with non-small cell lung cancer, and colorectal, prostate, cervical, and head and neck cancer.

Phase II studies of erlotinib at 150 mg/day have been performed in pre-treated patients with NSCLC, head and neck cancer, and ovarian cancer.100-102 Eligibility criteria in the NSCLC study included ≥10% expression of tumor cells with EGFR. Forty-four of 56 patients (78%) developed an acneiform rash (mild in 30, moderate in 13, severe in 1). Treatment was not halted in patients in this trial due to toxicity. Six patients (11%) achieved a partial response, confirmed at 12 weeks, 19 patients (34%) had stable disease, and 31 patients had disease progression. The median survival time in this study was 37 weeks, and the 1-year overall survival rate was 48%. All 6 responders in this trial developed an acneiform rash, versus 15 of 19 with stable disease, and 23 of 31 with disease progression. Antitumor response or stable disease was not associated with a higher percentage of tumor cells positive for EGFR.100 Additionally, response rates of 13% and 6% were seen in the phase II trials of refractory head and neck cancer and ovarian cancer, respectively, with the predominant toxicities, again, consisting of acneiform rash and diarrhea.101,102 The recently reported phase II study {n=57} (at a dose of 150 mg) is illustrative of erlotinib activity in NSCLC: “The objective response rate was 12.3% (95% CI, 5.1% to 23.7%). Responses were observed regardless of type or number of prior chemotherapy regimens. Median survival time was 8.4 months (95% CI, 4.8 to 13.9 months), and the 1-year survival rate was 40% (95% CI, 28% to 54%). Erlotinib therapy was associated with tumor-related symptom improvement. The drug was well tolerated; drug-related cutaneous rash and diarrhea were observed in 75% and 56% of patients, respectively. One patient experienced toxicity consisting of severe grade 3 rash and diarrhea. Time since diagnosis and good performance status were significant predictors of survival in a multivariate Cox proportional hazards model, whereas HER1/EGFR staining intensity was not. Additionally, survival correlated with the occurrence and severity of rash.”

Phase III trials of erlotinib, ovarian, and pancreatic cancers have been initiated. Results of two Phase III in NSCLC have been reported.104,105 These studies combined erlotinib (vs. placebo) with chemotherapy: Cisplatin and gemcitabine104 and carboplatin and paclitaxel.105 As might be expected there were no overlapping toxicities. The toxicity seen attributable to erlotinib was what would be expected for erlotinib alone: grade 3/4 rash and diarrhea (~6 and 10% respectively). There was no evidence for improved tumor responses, i.e., overall survival and time to progression with the addition of erlotinib.
Of note, erlotinib was recently approved for the treatment of metastatic NSCLC after first relapse.

1.7.3 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. This body is too large to summarize briefly here but has recently been reviewed by Harari and Huang. More recently Harari’s group has studied the relationship between radiation and erlotinib with regard to cell cycle, apoptosis, inhibition of EGFR auto-phosphorylation and Rad51 expression. These studies also incorporated Xenograft modeling, as well as cDNA microarray analysis of genes that may influence radiosensitization by erlotinib. Their results taken collectively highlight the capacity of erlotinib to enhance radiation at several levels, including cell cycle arrest, apoptosis induction, accelerated cellular repopulation, and DNA damage repair. These data support the concept that the combination of combination erlotinib/radiation represents a strategy worthy of examination in clinical trials.

1.8 Quality of Life

Quality of Life has become recognized as a critical endpoint in clinical oncology trials. 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.

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. Cella et al. more recently set out to measure a clinically meaningful change (CMC) utilizing this instrument. 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. 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. The first part of the EQ-5D consists of 5 items 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-
Quality adjusted survival is the weighted sum of different time in different health states added up to a total quality-adjusted survival time \[ U = \text{sum of quality (qi) of health states K times the duration (si) spent in each health state}. \]

Although developed in Europe, the EQ-5D has been used in the United States and Canada. Although developed in Europe, the EQ-5D has been used in the United States and Canada. 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. 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. 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 + erlotinib will have the largest QALYs by virtue of having the greatest tumor control and minimal tumor induced morbidity.

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 erlotinib, in conjunction with WBRT + SRS in a three-arm clinical trial.

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

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, cause of death (neurologic vs. other), and effects of non-protocol chemotherapy.

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

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

The contrast-enhancing intraparenchymal brain tumor must be well circumscribed and must have a maximum diameter of \( \leq 4.0 \) 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.

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. Patients who present with synchronous brain metastases at the time of the initial diagnosis of lung cancer are eligible.
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 Adequate bone marrow reserve (hemoglobin ≥ 8 grams, absolute neutrophil count ≥1000/mm³, platelets ≥ 100,000/mm³); Total bilirubin: within normal institutional limits other liver function tests (AST/SGOT, alkaline phosphatase, 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. If the liver function tests, specifically the alkaline phosphatase is elevated above the allowed limit, but this is deemed to be due to bone metastases and not liver metastases, the patient is eligible.
3.1.10 Patients randomized to receive erlotinib 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.
3.1.11 All patients on anticoagulants must be monitored closely—at least monthly.
3.1.12 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 (5/3/05) (4/6/06)
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 known or pre-existing 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.
3.2.15 History of allergic reactions attributed to compounds of similar chemical or biologic composition to erlotinib and temozolomide.
3.2.16 Previous temozolomide or erlotinib.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS (4/6/06)
(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.
4.3 Evaluation of metastatic disease to be performed as clinically indicated.
REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (7/14/05)(7/22/08)

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.

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

U.S. sites and Canadian sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.1.1 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

Note: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

Approved international sites fax copies of the documentation below, along with the completed International REC Certification Form, http://www.rtog.org/pdf_forms.html?members/forms=RTOG%20International%20REC%20Certification.doc to RTOG Headquarters (215-574-0300) prior to registration of the institution’s first case:
- REC approval letter;
- Informed Consent (English Version);
- Federalwide Assurance (FWA) number.

5.1.2 Pre-Registration Requirements for the Initial Shipment of Temozolomide:

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. After receipt of written approval of submitted LOI forms from RTOG Headquarters, International institutions must submit the SASF 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.

5.2 Registration (5/3/05)(7/22/08)

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:
- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to
An institution can register the patient by logging onto the RTOG web site (www.rtog.org), going to 'Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, as discussed in Section 5.2.2. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

5.2.2 Dial-in 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-RAO 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.) 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:

<table>
<thead>
<tr>
<th>Maximum Tumor Diameter</th>
<th>Assigned Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.0 cm</td>
<td>24 Gy</td>
</tr>
<tr>
<td>2.1-3.0 cm</td>
<td>18 Gy</td>
</tr>
<tr>
<td>3.1-4.0 cm</td>
<td>15 Gy</td>
</tr>
</tbody>
</table>

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 metastases, 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 QA 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(7/22/08)

6.8.1 Adverse Events (AEs) and Serious Adverse Events (SAEs) Reporting Requirements

(ARM 1) (7/14/05)(9/23/05)

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Therapy Evaluation Program (CTEP) via the Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:
- Death;
- A life-threatening adverse experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

AdEERS REPORTING REQUIREMENTS

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.info.nih.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html).
Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported to CTEP as indicated in the following tables using the AdEERS application. AdEERS can be accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup). Use the patient’s case number without any leading zeros as the patient ID when reporting via AdEERS. In order to ensure consistent data capture, AEs and SAEs reported using AdEERS must also be reported to RTOG on the AE case report form (see Section 12.1). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment.
CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR WITHIN 30 DAYS OF THE DATE OF THE LAST PROTOCOL TREATMENT

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CRITERIA FOR AdEERS REPORTING REQUIREMENTS FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS THAT OCCUR > 30 DAYS AFTER THE DATE OF THE LAST PROTOCOL TREATMENT

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- **Expedited AE reporting timelines defined:**
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following protocol treatment or procedure.

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

**RTOG REPORTING REQUIREMENTS**

AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only, both with and without a drug component arm. Events that occur on the RT-only arm of a study with a drug component must be reported for purposes of comparison. Events that occur on an RT-only study without a drug component also must be reported. Events involving RT-only must be reported via the AdEERS RT-only pathway.
This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA, version 6.0, for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page (http://ctep.info.nih.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html).

### Adverse Events (AEs) and Serious Adverse Events (SAEs)

Adverse Events (AEs) and Serious Adverse Events (SAEs) that meet the criteria defined above experienced by patients accrued to this protocol must be reported via AdEERS. SAEs must be reported within 24 hours of discovery of the event. Contact the CTEP Help Desk if assistance is required.

All supporting source documentation being faxed to NCI, must be properly labeled with the RTOG study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated AE/SAE FAX, 215-717-0990, before the 5- or 10-calendar-day deadline. All forms submitted to RTOG Headquarters also must include the RTOG study/ case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

### 6.8.2 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or 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.cancer.gov/forms/index.html. 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 a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

### 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.

**Drug Information**

Temozolomide belongs to a group of compounds known as imidazotetrazinones. Its chemical name is 3, 4-dihydro-3-methyl-4-oximidazo[5, 1-d]-as-tetrazine-8-carboxamide. The material is a white to light tan/light pink powder with a molecular formula of C_{6}H_{10}N_{6}O_{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.

**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\textsuperscript{6} and N\textsuperscript{7} positions of guanine.

**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 $T_{\text{max}}$ 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 AIC 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/m².

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/m² 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/m²). 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 $C_{\text{max}}$ 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, H₂-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 (4/6/06)

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.

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 (5/3/05)(7/22/08): 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 for US and Canadian sites 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. This must be done prior to registration of the institution’s first case.

**Note:** International sites must receive written approval of submitted LOI Forms from RTOG Headquarters prior to submitting documents to local ethics committee for approval. See [http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc](http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc). Approved international 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 temozolomide 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. Canadian and International shipments may require additional time. RTOG will notify I.V. Solutions, Inc. to initiate each of these shipments after registration of the patient. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

At the close of the study, unused, unopened, non-expired drug marked clearly with the institution number of the site returning the agent and the quantity being returned should be returned to I.V. Solutions. All other drug can be destroyed or disposed of at the site according to institutional policy. The equivalent of a faxed or mailed memo or e-mail from the responsible party to I.V. Solutions specifying this was done with the institution number and quantity destroyed included will be required. In a case where drug expires and requires replacing, the drug can be destroyed on site and reordered through the normal reorder procedure noting the re-supply is to replace the destroyed expired drug.

Additional questions about supply and delivery should be directed to:

Angelo Corradino, R.Ph
I.V. Solutions, Inc.
162 North Main Street
Old Forge, PA 18518
(570) 457-9201
Fax (570) 457-0465
ivspublic@choiceonemail.com

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/m²/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 (5/8/07)
After WBRT, the protocol allows four options: 1) continue the temozolomide alone; 2) continue temozolomide in conjunction with other chemotherapy; 3) discontinue the
temozolomide and initiate other chemotherapy at the investigator's discretion; or 4) discontinue temozolomide and not receive other chemotherapy. If the patient continues temozolomide, then four weeks after completion of WBRT treatment, the patient will be treated at 200 mg/m²/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/m²/day for 5 days. Treatment cycles shall be repeated every 28 days following the first daily dose of study drug from the previous cycle, until progression or for a maximum of 6 additional cycles or until the drug is discontinued at the investigator's discretion. 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.)

Patients who present with synchronous brain metastasis(es) and systemic disease are eligible. If these patients are randomized to the temozolomide arm, they may receive, after the three-week period of WBRT/temozolomide, the following:

1) temozolomide alone, or
2) temozolomide in combination with chemotherapy as defined by the protocol (section 9.3), or
3) appropriate chemotherapy alone or in combination with non-CNS radiotherapy, at the discretion of the investigator.

7.1.8.4 Criteria for Continuing Temozolomide (4/6/06):
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 \( \geq 1,200 / \text{mm}^3 \) and platelet count is \( \geq 100,000 / \text{mm}^3 \), then repeat cycles may be administered according to the dose modification guidelines in Section 7.1.8.5; 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 \( 1,200 / \text{mm}^3 \). If these hematological criteria are met, study drug may be administered according to the dose adjustments outlined in Section 7.1.8.5.1.

If ANC remains < \( 1200 / \text{mm}^3 \) or platelet count < \( 100,000 / \text{mm}^3 \) two 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.

7.1.8.5 Dose Modification Guidelines (4/6/06):
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*

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<tr>
<td>0</td>
<td>75 mg/m^2/d</td>
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<tr>
<td>-1</td>
<td>60 mg/m^2/d</td>
<td>qd during RT</td>
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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)

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<td>0</td>
<td>200 mg/m^2/d</td>
<td>d1-5 q 28 d</td>
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<tr>
<td>-1</td>
<td>150 mg/m^2/d</td>
<td>d1-5 q 28 d</td>
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<tr>
<td>-2</td>
<td>100 mg/m^2/d</td>
<td>d1-5 q 28 d</td>
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Subjects who require dose reductions to a dose level of <100 mg/m^2/d of study drug will be removed from protocol treatment.

7.1.8.5.1 Hematologic Criteria for Dose Modification (4/6/06):

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 100 mg/m^2/day, etc.).

Dose Adjustment Criteria

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

There are no dose escalations allowed.

7.1.8.5.2 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 (5/3/05)(5/8/07):**
- Investigator's discretion, after WBRT.
- 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 whole brain radiotherapy, temozolomide may be discontinued and any other chemotherapy regimen (as long as it does not include erlotinib) 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 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 Erlotinib (NSC # 718781; IND # 63383) (5/3/05)
See package insert and Investigator's Brochure for further information. Investigator's Brochures may be obtained from PMB for investigational agents where CTEP holds the IND. To receive an Investigator's Brochure, you must be an active participant on a NCI sponsored clinical trial or have an approved letter of intent for a protocol (LOI) and have an active investigator registration status. Contact the IB Coordinator at IBCoordinator@mail.nih.gov or 301-496-5725, Monday through Friday, from 8:30 a.m. to 4:30 p.m. Eastern time.

7.2.1 Drug Information:
- OSI-774 (free base)
- OSI-774-01 (hydrochloride salt) [formulation used for clinical evaluation]
- Chemical Name: N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride
- Other Names: CP-358, 774, USAN: erlotinib hydrochloride, Tarceva™
- Classification: Tyrosine kinase inhibitor (EGFR)

Molecular Formula: C_{22}H_{23}N_{3}O_{4}  M.W.: 393.4 (free base)  429.9 (hydrochloride salt)

Mechanism of Action: OSI-774 is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase.

Pharmacokinetics: Erlotinib is about 60% absorbed after oral administration. The bioavailability is increased by food to almost 100%. Its half-life is about 36 hours and it is cleared by CYP3A4 metabolism.

Pre-clinical Pharmacology: OSI-774 inhibits the human EGFR tyrosine kinase with an IC_{50} of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact
tumor cells with an IC\textsubscript{50} of 20 nM (7.9 ng/mL). OSI-774 inhibits EGF-dependent proliferation of cells at sub micromolar concentrations and blocks cell-cycle progression in the G\textsubscript{1} phase.

7.2.2 Supply, Storage, and Stability (5/3/05)
Erlotinib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Erlotinib is provided to the NCI under a Clinical Trials Agreement (CTA) between OSI Pharmaceuticals, Inc. and the DCTD, NCI.

Erlotinib is supplied as 25 mg, 100 mg, and 150 mg white film-coated tablets. In addition to the active ingredient, OSI-774, the tablets contain lactose, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate. Tablets are unmarked and unscored. The 25mg tablets (1/4 inch diameter, 3 mm deep (formerly non-film-coated)), 100 mg tablets (11/32 inch in diameter, 5 mm deep), and 150mg tablets (13/32 inch in diameter, 5.1 mm deep) are supplied 30 tablets/bottle.

The intact bottles should be stored at controlled room temperature (15°C – 30°C). Shelf life surveillance studies of the intact bottle are on-going. Current data indicate erlotinib is stable for at least 3 years at room temperature.

All investigational products must be kept in a secure place under appropriate storage conditions. All trial treatment products will be stored in a lockable storage area and protected from light.

7.2.3 Agent Ordering
Erlotinib 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.
7.2.6 Method of Administration:
7.2.6.1 Tablets should be taken once daily preferably in the morning with up to 200 mL of water 1 hour before or 2 hours after food.

7.2.6.2 Administration through G-tube: The tablets required for the dose should be dissolved in 100 mL of sterile water. The dissolved tablets should be shaken vigorously to form a uniform suspension. The suspension should be drawn up into a syringe and administered through the G-tube port. Repeat the syringe transfer until the entire volume has been administered. A small volume (40 mL) of sterile water should be added to the container used to dissolve the tablets and the residual suspension should be shaken, aspirated into syringe, and administered. This last step should be repeated to ensure the entire dose is administered. The total volume of delivery/rinse (as per procedure submitted to IND) is ~180 mL.

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

7.2.7 Treatment
7.2.7.1 Erlotinib during Whole Brain Radiotherapy
Erlotinib will be administered orally, once a day, beginning on day one of WBRT (whole brain radiotherapy) at 150 mg/day. Erlotinib tablets should be taken once daily preferably in the morning with up to 200 mL of water 1 hour before or 2 hours after food.

No other chemotherapy agent will be administered during this time.

7.2.7.2 Erlotinib after Whole Brain Radiotherapy (5/8/07)
Erlotinib will be continued orally, once a day, after completion of WBRT (whole brain radiotherapy) at 150 mg/day. Treatment shall be continued until CNS progression or a maximum of 6 months after completion of WBRT + SRS; or erlotinib may be discontinued after the whole brain radiation therapy at the investigator’s discretion. The investigator is encouraged but not required to give at least 2 months erlotinib post-radiotherapy.
chemotherapeutic agents (as long as the regimen does not include temozolomide) may be initiated at any time 4 weeks after completion of whole brain radiotherapy.

**7.2.7.3 Potential Drug Interactions (5/3/05)(4/24/09):**

The enzymes responsible for formation of the major metabolites in humans were identified as cytochromes P450 3A4 and 3A5 (expressed in liver) and 1A1 (expressed in lung). Studies on the inhibition potential of OSI-774 and its major metabolite OSI-420, on the main human cytochrome P450 isoenzymes revealed a relatively strong inhibition of CYP 3A4 by OSI-774 (Ki 8 μM) and a weak inhibition of CYPs 1A2 and 3A4 by OSI-420 (Ki 20 μM). This suggests that OSI-774 could reduce the clearance of co-administered drugs whose metabolism is dependent on these P450 cytochrome isoenzymes.

Erlotinib is both protein bound (92% to 95%) and metabolized by CYP3A4. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein-bound or CYP3A4 inhibitors or inducers.

There is a potential interaction between erlotinib and warfarin. Patients have experienced elevated INRs and bleeding with this combination of drugs. Patients on warfarin and erlotinib 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 erlotinib).

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.

**Proton Pump Inhibitor:** Erlotinib’s solubility decreases as the pH increases. Co-administration of omeprazole with erlotinib will decrease the AUC and C\text{max} by 46% and 61%, respectively.

**H\textsubscript{2}-antagonist:** Avoid concomitant use of erlotinib with gastric acid-reducing agents if possible. When ranitidine 300 mg is given with erlotinib, erlotinib AUC and C\text{max} decrease by 33% and 54%, respectively. Increasing the dose of erlotinib will not compensate the loss of exposure. However, if an H\textsubscript{2}-antagonist receptor is needed, take erlotinib at least 2 hours before or 10 hours following the H\textsubscript{2}-antagonist administration. Dosing such, erlotinib loss of exposure is minimized to AUC of 15% and C\text{max} of 17%.

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3. Alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, an erlotinib dose should be discussed with the PI.

Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. Caution should be used when administering or taking erlotinib with ketoconazole and other strong CYP3A4 inhibitors. See Appendix VII.

Grapefruit juice may change the level of erlotinib in the blood. Therefore, patients must be advised to avoid grapefruit while taking erlotinib.

**7.2.8 Adverse Events and Dose Modification Guidelines (4/6/06)(10/15/08)(4/24/09)**

Initial clinical results indicate that nausea, headache, emesis, fatigue, diarrhea, and skin adverse events described as dry skin, exfoliative dermatitis, pruritus and rash may occur in >10% of patients treated with erlotinib. Rash or dermatosis (CTCAE grade 1-3) has been reported in many subjects (~50%) during the first several days of treatment, although severity diminishes after 4 weeks of therapy. The use of topical agents (i.e., diphenhydramine, corticosteroids) and oral antibiotics (tetracycline) has been instituted in some patients with variable results. In patients with severe rash, treatment has been discontinued or the study drug dose reduced. The etiology of the rash is still unknown, but may be related to the mechanism of action of erlotinib.
Nausea and diarrhea (Grade 1-2) have been observed in approximately half of all subjects treated with erlotinib. Both adverse events are transient and usually do not require a reduction in dosage.

Diarrhea is well controlled in most patients by either the use of loperamide or dose reduction.

There is the possibility of occurrence of pulmonary events, specifically interstitial pneumonia and pneumonitis. Patients with worsening pulmonary symptoms or new onset or worsening dyspnea, cough, or fever should be promptly evaluated for interstitial pneumonitis and treated as clinically indicated. Erlotinib should be temporarily discontinued pending diagnosis of the nature of the pulmonary disorder. Erlotinib should be permanently discontinued if a diagnosis of interstitial pneumonitis/pneumonia is confirmed and is considered to be related to erlotinib.

**Gastrointestinal Perforation:** Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed infrequently. Some cases had a fatal outcome. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease, are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation.

**Bullous and Exfoliative Skin Disorders:** Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions.

**Ocular Disorders:** Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment and are known risk factors for corneal perforation/ulceration. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Fertility and teratology studies with erlotinib have not been conducted, and safety for women of childbearing capacity cannot be implied from the existing data.

For adverse events that are thought to be related to erlotinib, the daily dose of erlotinib will be decreased according to the schedule displayed in the Table 1.

a) Grade 2 diarrhea and skin rash do not require temporary discontinuation of treatment as these adverse events may improve despite continued treatment. For Grade 2 skin rashes and diarrhea that are unacceptable to the patient for symptomatic reasons, erlotinib should be temporarily held until resolution < grade 1 and subsequently re-started at the same dose. If symptomatic grade 2 diarrhea and skin rash recur after re-instituting treatment at the 150 mg daily dose and require temporary discontinuation, treatment should be held until resolution to < grade 1 and re-instituted at a reduced dose (see Table 1). For grade 2 non-hematological toxicity that is medically concerning (e.g. prolonged cardiac, pulmonary, or neurotoxicity), treatment should be held until resolution ≤ grade 1 and re-instituted at a reduced dose.

b) For Grade 3 and 4 adverse events, discontinue treatment and re-evaluate at least weekly until resolution to ≤ grade 1 and then re-institute at a reduced dose.

c) Patients with unresolved adverse events after 2 weeks should be taken off protocol treatment. However, if it is the treating physician opinion that the patient may benefit from continued treatment the patient may continue on study. Patients may have a second dose reduction for toxicity; however, patients requiring a third dose reduction should be taken off protocol treatment unless, in the opinion of the treating physician, there is reason to believe the patient may benefit from continued treatment. The decision to proceed with treatment should be made in consultation with the CTEP drug monitor.

d) Once a dose has been reduced for a patient, it should not be subsequently increased.
Table 1

Erlotinib Dose Level Reductions

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>First Reduction</th>
<th>Second Reduction</th>
<th>Third Reduction(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg/day</td>
<td>100 mg/day</td>
<td>75 mg/day</td>
<td>50 mg/day</td>
</tr>
</tbody>
</table>

(a) after discussion with CTEP monitor
Table 2 outlines erlotinib dosage modification criteria for erlotinib–related adverse events as well as guidelines for their management.

**Table 2. Dose Reduction criteria and guidelines for management of erlotinib related adverse events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Guideline for management</th>
<th>Erlotinib dosage modification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis</td>
<td>1</td>
<td>No intervention</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2 (if &lt; 14 days)</td>
<td>Preservative-free artificial tears, ointments, and/or other therapies as clinically indicated, with a follow-up examination within 2 weeks</td>
<td>Hold until recovery to ≤ grade 1 And then Reduce 1 dose level</td>
</tr>
<tr>
<td></td>
<td>2 (if &gt;14 days)</td>
<td></td>
<td>None**</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td></td>
<td>Hold until recovery to ≤ grade 1 And then Reduce 1 dose level*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>No intervention</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Loperamide (4 mg at first onset, followed by 2 mg every 2–4 hrs until diarrhea free for 12 hrs)</td>
<td>Hold until recovery to ≤ grade 1 And then Reduce 1 dose level*</td>
</tr>
<tr>
<td></td>
<td>≥ 3 (despite optimal use of loperamide)</td>
<td></td>
<td>None**</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>No intervention</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Any of the following: minocycline*, topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)</td>
<td>Hold until recovery to ≤ grade 1 And then Reduce 1 dose level</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td></td>
<td>None**</td>
</tr>
<tr>
<td>Signs and symptoms of Interstitial Pneumonitis</td>
<td>Patient should be thoroughly evaluated, closely monitored, and supported as clinically indicated.</td>
<td>Hold pending diagnosis Permanently discontinue if diagnosis is confirmed and considered possibly related to OSI-774</td>
<td></td>
</tr>
<tr>
<td>Other toxicity</td>
<td>≥ 2 prolonged clinically significant toxicity</td>
<td>Treatment as appropriate</td>
<td>Hold until recovery to ≤ grade 1 And then Reduce 1 dose level*</td>
</tr>
<tr>
<td>Liver transaminases</td>
<td>≥Grade 3 (i.e. &gt;5x ULN)</td>
<td>Treatment as appropriate</td>
<td>Omit until grade 0-2 then ↓ dose by the following dose levels according to current treatment dose (150 mg → 100 mg → 75 mg).*</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>≥Grade 3 (i.e. &gt;3x ULN)</td>
<td>Treatment as appropriate</td>
<td>Omit until grade 0-2 then ↓ dose by the following dose levels according to current treatment dose (150 mg → 100 mg → 75 mg).*</td>
</tr>
<tr>
<td>GI/bowel perforation</td>
<td></td>
<td>Treatment as appropriate</td>
<td>Discontinue erlotinib</td>
</tr>
<tr>
<td>Ocular adverse events</td>
<td></td>
<td>Treatment as appropriate</td>
<td>Interrupt erlotinib for acute/worsening eye pain. Discontinue erlotinib in patients with persistent inflammation or severe eye surface damage.</td>
</tr>
</tbody>
</table>
Note: Only two dose reductions are allowed.
* if no recovery after 2 weeks of holding drug, patients should go off study
** if dose has been previously held for grade 2 rash or diarrhea, and grade 2 symptoms recur, OR if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce dose one level
+ recommended dose: 200mg po bid (loading dose), followed by 100mg po bid for 7-10 days
The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. Frequency is provided based on 3622 patients. Below is the CAEPR for erlotinib (OSI-774).

### Adverse Events with Possible Relationship to Erlotinib (OSI-774)  
**(CTCAE v3.0 Term)**  
**[n=3622 patients]**

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSTITUTIONAL SYMPTOMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue (asthenia, lethargy, malaise)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DERMATOLOGY/SKIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair loss/aloepecia (scalp or body)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus/itching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>Rash: acne/acneiform</td>
<td>Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)</td>
</tr>
<tr>
<td></td>
<td>Rash: hand-foot skin reaction</td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry mouth/salivary gland (xerostomia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heartburn/dyspepsia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis (clinical exam) - Select</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis (functional/symptomatic) - Select</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Perforation, GI - Select</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Taste alteration (dysgeusia)</td>
<td></td>
</tr>
<tr>
<td><strong>HEMORRHAGE/BLEEDING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage, pulmonary/upper respiratory - Nose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage, GI - Select</td>
<td>Hemorrhage, CNS</td>
<td></td>
</tr>
</tbody>
</table>

**EXPECTED AEs FOR ADEERS REPORTING**  
Agent Specific Adverse Event List (ASAEL)

- Fatigue (asthenia, lethargy, malaise)
- Dry skin
- Hair loss/aloepecia (scalp or body)
- Nail changes
- Pruritus/itching
- Rash/desquamation
- Rash: acne/acneiform
- Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Rash: hand-foot skin reaction
- Anorexia
- Dehydration
- Diarrhea
- Dry mouth/salivary gland (xerostomia)
- Heartburn/dyspepsia
- Mucositis/stomatitis (clinical exam) - Select
- Mucositis/stomatitis (functional/symptomatic) - Select
- Nausea
- Perforation, GI - Select
- Taste alteration (dysgeusia)
- Vomiting
- Hemorrhage, CNS
This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on erlotinib (OSI-774) trials but with the relationship to erlotinib (OSI-774) still undetermined:

**BLOOD/BONE MARROW** - Lymphopenia; Platelets

**COAGULATION** - DIC (disseminated intravascular coagulation); INR (International Normalized Ratio of prothrombin time; in patients taking Coumadin)

**DERMATOLOGY/SKIN** - Urticaria (hives, welts, wheals)

**GASTROINTESTINAL** - Colitis; Constipation; Dysphagia (difficulty swallowing); Esophagitis; Gastritis (including bile reflux gastritis); Pneumatosis; Ulcer, GI - Select

**HEPATOBILIARY/PANCREAS** - Cholecystitis; Pancreatitis

**LYMPHATICS** - Edema: limb

**METABOLIC/LABORATORY** - Calcium, serum-low (hypocalcemia); Creatinine; Glucose, serum-high (hyperglycemia); Magnesium, serum-low (hypomagnesemia); Phosphate, serum-low (hypophosphatemia); Potassium, serum-high (hyperkalemia); Potassium, serum-low (hypokalemia); Sodium, serum-low (hyponatremia)

**MUSCULOSKELETAL/SOFT TISSUE** - Muscle weakness, generalized or specific area (not due to neuropathy - Whole body generalized)

**NEUROLOGY** - Confusion; CNS cerebrovascular ischemia; Dizziness; Neuropathy: sensory

**OCULAR/VISUAL** - Vision, blurred vision; Ocular/visual - Other (orbital cellulitis); Uveitis; Watery eye (epiphora, tearing)
PAIN - Pain - Throat/pharynx/larynx
PULMONARY/UPPER RESPIRATORY - Adult Respiratory Distress Syndrome (ARDS)
RENAL/GENITOURINARY - Renal failure
VASCULAR - Thrombosis/thrombus/embolism

**Note:** Erlotinib (OSI-774) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

**Note:** Erlotinib (OSI-774) induced diarrhea and/or vomiting has been associated with dehydration, hyperkalemia; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia, increased creatinine, and renal failure.

**Note:** Erlotinib induced rash has been associated with secondary infections of skin such as folliculitis and cellulitis.

**Note:** Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of erlotinib (OSI-774) in patients with baseline hepatic impairment.

### 7.2.10 Combining chemotherapy agents with erlotinib (4/24/09)

Phase III trials of erlotinib, ovarian, and pancreatic cancers have been initiated. Results of two Phase III in NSCLC have been reported.\(^\text{104,105}\) These studies combined erlotinib (vs. placebo) with chemotherapy: Cisplatin and gemcitabine\(^\text{104}\) and carboplatin and paclitaxel.\(^\text{105}\) As might be expected there were no overlapping toxicities. The toxicity seen attributable to erlotinib was what would be expected for erlotinib alone: grade 3/4 rash and diarrhea (~6 and 10% respectively). There was no evidence for improved tumor responses, i.e., overall survival and time to progression with the addition of erlotinib.

### 7.2.11 Preclinical safety:

The major effects attributed to erlotinib in toxicology studies involved the hepatobiliary, gastrointestinal and renal systems which in turn resulted in secondary hematopoietic changes. Treatment related decreases in food consumption and body weight gain, considered secondary to a decrease in gastric emptying, were observed in the rat at 5mg/kg/day in a 1-month study. In a 6-month study this dose resulted in elevations in serum levels of bilirubin and transaminases, papillary necrosis, ovarian atrophy and hair follicle degeneration. At 10mg/kg/day there was also an increase in kidney and adrenal weights, the latter associated with angiectasis, and hepatocyte necrosis. Plasmocytosis occurred in cervical lymph nodes. The No-Observed Adverse Effect Level (NOAEL) in the rat was 1mg/kg/day.

Erlotinib produced a low incidence of emesis in dogs and in a 12-month study a dose of 15mg/kg/day resulted in reduced body weight gain. A higher dose of 50mg/kg/day was associated with marked toxicity, which precluded dosing beyond 14 days. This was associated with marked corneal edema, ulceration and perforation, which were reversible once treatment was terminated. Gastrointestinal and renal toxicities and abnormal liver function tests were also observed. The NOAEL level in this study was 7.5mg/kg/day.

An exploratory toxicology study in the cynomolgus monkey resulted in emesis and loose stools at 100mg/kg/day when dosed for a period of 7 days. Dosing at 200mg/kg/day for the same period of time resulted in raised serum bilirubin. One animal died. Dosing at 400mg/kg/day was not tolerated beyond 4 days of dosing. Skin lesions were evident and serum bilirubin was elevated.

Erlotinib does not induce microbial or mammalian cell gene mutations *in vitro* and does not produce chromosomal aberrations *in vitro* and *in vivo*. No studies to assess the effects of erlotinib on reproductive function and teratogenicity or the potential for carcinogenicity have been performed thus far.

Erlotinib can increase serum levels of bilirubin due to its ability to inhibit UGT1A1 – the enzyme responsible for bilirubin conjugation and subsequent clearance.
7.3 Clinical Trials Agreement (5/3/05)

The agent(s) ([hereinafter referred to as “Agent(s)”]) erlotinib used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) between OSI Pharmaceuticals, Inc.([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 Events (7/14/05)(7/22/08)

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA 6.0 for grading of all 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.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.6.1 Adverse Events (AEs)

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note:** AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.X also must be reported via AdEERS.

**NOTE:** If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.6.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies:** All unexpected potentially related SAEs
- **Phase I Studies:** All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship
**Definition of an SAE:** Any adverse drug experience occurring at any dose that results in any of the following outcomes:

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Any non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the Patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6.3 **Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

AML or 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](http://ctep.cancer.gov/forms/index.html) available at the [NCI/CTEP Secondary AML/MDS Report Form](http://ctep.cancer.gov/forms/index.html). 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 a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
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<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
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<tr>
<td>Philadelphia, PA 19103</td>
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### AdEERS Expedited Reporting Requirements (7/14/05)

#### Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or a non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days\(^1\) of the Last Dose of the Investigational Agent [Erlotinib] [Arm 3] or Temozolomide [Arm 2] in this Study

<table>
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<tr>
<td>10 Calendar Days</td>
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<td>10 Calendar Days</td>
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</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:

- **AdEERS 24-hour notification** followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
  - AdEERS 10 calendar day report:
    - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
    - Grade 5 unexpected events

\(^2\) Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

---

**Note:** All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- **Expedited AE reporting timelines defined:**
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

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

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**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND or a non-CTEP IND:**

Not 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 anti-emetics 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) (5/3/05):
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 erlotinib, either singly or in other combinations.

9.3.2 Arm 2 (temozolomide)(5/3/05)(5/8/07)(7/22/08):
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.

Patients who present with synchronous brain metastasis(es) and systemic disease are eligible. If these patients are randomized to the temozolomide arm, they may receive, after the three-week period of WBRT/temozolomide, the following:
1) Temozolomide alone, or
2) Temozolomide in combination with chemotherapy as defined by the protocol (Section 9.3), or
3) Appropriate chemotherapy alone or in combination with non-CNS radiotherapy, at the discretion of the investigator.

Phase I data (see Section 1.6) are available to support the following three regimens in combination with temozolomide:
docetaxel 80 mg/m² i.v. Day 1
paclitaxel 175 mg/m² i.v. Day 1
cisplatin 75-100 mg/m² i.v. Day 1
Temozolomide dose should be reduced to 150mg/m² 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/m² Days 1 to 5
- + gemcitabine: 1,000 mg/m² Days 1, 8
- + vinorelbine: 25 mg/m² Days 1, 8

**OR**

- temozolomide: 150 mg/m² Days 1 to 5
- + gemcitabine: 1,000 mg/m² Days 1, 8
- + cisplatin: 50 mg/m² 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 (erlotinib) (5/3/05)(5/8/07):**
Chemotherapy for treatment of systemic disease should be withheld during the radiation phase of protocol treatment. After radiation, the erlotinib may be continued for a maximum of 6 months or discontinued at the investigator’s discretion. No other treatment specifically for brain metastases should be given until a recurrence is detected. After completion of whole brain radiotherapy, any other chemotherapy regimen (as long as it does not include temozolomide) is permitted.

**9.4 Anticonvulsants (5/3/05)**

9.4.1 A patient who has been randomized to receive erlotinib may not be on an enzyme-inducing anti-convulsant medication (phenytoin, carbamazepine, phenobarbital, 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 of erlotinib. 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: 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 erlotinib 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 (5/3/05)
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 erlotinib is started.

9.7.4 Antidiarrheals (5/3/05)
Previous trials have shown that the frequency and severity of diarrhea rarely hindered administration of erlotinib and could be managed with loperamide. The recommended dose is loperamide 4 mg at first onset, followed by 2 mg q 2–4 hours until diarrhea free for 12 hours.

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.

9.7.8 Antibiotics (5/3/05)
In some patients, rash appeared to be treatable with standard acne therapies, including topical and oral antibiotics used to treat acne. Anecdotal reports of improvement have occurred with any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course).

9.7.9 Patients are recommended to wear sun screen protection, hat, and long sleeves to avoid sun as it can exacerbate skin rash. (4/24/09)

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 (9/23/05) (4/6/06)

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a. BrCS (brain) and LCS (lung) cancer symptom subscales and the EQ-5D to be obtained pre-registration, 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.
e. On days 8 and 15 during radiation with temozolomide; on days 21 and 28 during post radiation period.

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. 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. 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.

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 has been established. 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)(5/3/05)

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

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 (5/3/05)

- 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)
- Effects of non-protocol chemotherapy

13.2 Sample Size and Power Calculation

13.2.1 Primary Endpoint (5/3/05)

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 erlotinib, 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% increase in MST from 5.9 months on the control arm to 8.9 months on either of the experimental arms.

East-3 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 a 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
These weights will be used to calculate quality-adjusted survival for each patient.

\[ WS = \sum_{t=0}^{T} [V(t) \cdot Q(t)] \]

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 (5/3/05): 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 = 5.9 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 \( \chi^2 \) 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, \( \Delta^2 = \sum(\pi_{2j} - \pi_{1j})^2 / [2(\pi_{2j} - \pi_{1j})] \), of 0.0702.

### 13.2.2.4 Change in Performance Status at Six Months

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 \( \chi^2 \) test will have 90% power to distinguish between the groups when the proportions in the 3 categories are characterized by an effect size, \( \Delta^2 = \sum(\pi_{2j} - \pi_{1j})^2 / [2(\pi_{2j} - \pi_{1j})] \), of 0.0586.

### 13.2.2.5 Change in Steroid Dose at Six Months (5/3/05)

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 = 5.9 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, a 0.050 level \( \chi^2 \) test will have 90% power to distinguish between the groups when the proportions in the 3 categories are characterized by an effect size, \( \Delta^2 = \sum(\pi_{2j} - \pi_{1j})^2 / [2(\pi_{2j} - \pi_{1j})] \), of 0.1217.

### 13.2.2.6 Cause of Death

See Section 11.5 for the definition of neurologic death. For the comparison of cause of death (neurologic vs. other), a two group \( \chi^2 \) 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.

### 13.2.2.7 Effects of non-protocol chemotherapy (5/3/05)

An exploratory analysis of the effects of possible non-protocol chemotherapy will be undertaken. This analysis will be done in two ways. First, comparisons of arm 1 to arm 2 and arm 1 to arm 3 will be made in the subgroup of eligible patients that were treated as per the treatment assigned to them at randomization and that also received additional
chemotherapy as per Section 9.3 of the protocol. These comparisons will be done using the same methods as described in Section 13.5.1 of the protocol. The projected power of such analyses will depend upon the number of patients excluded, and will be no greater than 85%. Additionally, a multivariate analysis will be made in all eligible patients using the method described in Section 13.5.1 of the protocol, with assigned treatment, RPA class, number of mets, and extent of extracranial disease as fixed covariates along with a time dependent covariate of when non-protocol chemotherapy was initiated.

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. The stratifying variables are RTOG RPA class (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 0-1 and 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. The log-rank test will be used to compare survival between two treatment arms. 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. 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 \( \chi^2 \) 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 \(^{135}\) 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\%. \(^{136}\) 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 (7/14/05)
This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.7 Gender and Minorities (7/22/08)
In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities 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. \(^{131}\) 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:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>172</td>
<td>194</td>
<td>366</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total</strong></td>
<td>179</td>
<td>202</td>
<td>381</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Black or African American</td>
<td>20</td>
<td>22</td>
<td>42</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>155</td>
<td>176</td>
<td>331</td>
</tr>
<tr>
<td><strong>Racial Category: Total</strong></td>
<td>179</td>
<td>202</td>
<td>381</td>
</tr>
</tbody>
</table>
REFERENCES (5/3/05)


127. Investigator's Brochure, Schering Oncology Biotech, Lancaster, NY 14086


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 ERLOTINIB IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND 1-3 BRAIN METASTASES (5/3/05)

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 study doctor. (5/3/05)

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?(5/3/05)

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, erlotinib 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? (5/3/05) (4/6/06)(5/8/07)

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 erlotinib
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 up to a maximum of 6 months after radiation. You or your doctor may choose to stop the drug at any time. Temozolomide should be taken with water on an empty stomach. It is best to take it at bedtime.
Erlotinib: This is a drug you will take daily during radiation and for 6 months after radiation. You or your doctor may choose to stop the drug at any time. Erlotinib should be taken with water preferably in the morning 1 hour before or 2 hours after food.

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

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>History, Physical and Neurological Exam</td>
<td>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.</td>
</tr>
<tr>
<td>Blood Counts, Chemistries</td>
<td>Prior to study entry, during drug treatment and after the radiation treatment period.</td>
</tr>
<tr>
<td>Pregnancy test (if applicable)</td>
<td>Prior to study entry</td>
</tr>
<tr>
<td>Brain MRI with contrast</td>
<td>Prior to study entry, at month 3, 9, 12, every 3 months in year 2, and every 6 months thereafter</td>
</tr>
<tr>
<td>Quality of Life Questionnaires</td>
<td>Prior to study entry, month 3, month 6, month 9, month 12, month 18, and month 24 (9/23/05)</td>
</tr>
</tbody>
</table>

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 erlotinib 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
- Erlotinib is FDA approved for the 2\textsuperscript{nd} line treatment (the most effective treatment after the first treatment has failed) of NSCLC (Non-Small Cell Lung Cancer)

Both drugs have been used in patients with central nervous system tumors and preliminary evidence suggests they may be of benefit. (5/3/05)

**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: (5/3/05)**
(Both temozolomide and erlotinib 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 (7/14/05)(5/8/07)(7/22/08):

Likely
• Nausea and/or Vomiting
• Constipation
• Lowered white blood cell counts (may make you more likely to get an infection)
• Lowered red blood cell counts (may make you feel tired or weak)
• Lowered platelet counts (may make you more likely to bruise or bleed)

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
- Death

Patients treated with temozolomide capsules may rarely experience low blood counts for a prolonged period of time. This unusual result can be life threatening and fatal. The more typical situation is for blood counts to recover quickly (in a week or two) if they decrease after receiving temozolomide. In the rare situations, when this complication has been observed, patients are often taking other drugs, which can rarely cause this same complication. (These drugs include carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim).

Another life threatening complication, which has been rarely observed, is the development of leukemia (a form of cancer of the blood). When this has been observed (in patients that have received temozolomide) these same patients have also been exposed to other chemotherapy drugs as well as radiation, which are also known to rarely cause leukemia. Thus, the precise relationship of temozolomide to the development of leukemia is not clear. If you have questions or concerns regarding these potential severe side effects, please discuss them with your physician.

Temozolomide capsules should not be opened. (5/3/05)

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 may receive a preventive medicine.
There is the potential for multi-system organ failure in any patient with cancer, and thus consideration of drug interactions is important. To avoid potential drug interactions, you should consult your physician or pharmacist before taking any new medications, including over the counter (non-prescription) medications.

**Risks Associated with Erlotinib** (5/3/05)(7/14/05)(5/8/07)(10/15/08)(4/24/09)

**Likely:**
- Fatigue or tiredness
- Rash/flaking or shedding of outer layer of skin
- Loss of appetite
- Diarrhea
- Vomiting

**Less Likely:**
- Dry skin
- Hair loss
- Nail changes
- Itching
- Acne; pimples
- A condition in which your body does not have as much water and fluid as it should (dehydration, which can be caused by severe diarrhea and/or vomiting)
- Dry mouth
- Heartburn
- Irritation or sores in the lining somewhere in the digestive tract
- Nausea, the urge to vomit
- Taste changes
- Nosebleed
- Bleeding in some organ(s) of the digestive tract
- Infection(s) somewhere in the body
- Increased level of a liver enzyme (ALT/SGPT; AST/SGOT)
- Abnormal liver or bone enzyme level (alkaline phosphatase)
- Elevation of a liver pigment (bilirubin) in the blood indicative of liver dysfunction
- Dry eye
- Damage to the surface of the eye
- In-grown eyelashes/thickening of eyelashes
- Belly pain
- Head pain/headache
- Cough
- Shortness of breath
- Inflammation of the lungs (pneumonitis, which can rarely be life-threatening or fatal)

**Rare, But Serious:**
- Severe reaction of the skin and gut lining that may include rash and shedding, or death of tissue
- Inflammation of the skin on the palms of the hands and soles of the feet
• A hole in a part(s) of the digestive tract (which commonly requires surgery and can be life-threatening or fatal)
• Bleeding in the brain or spinal cord
• Liver problems/liver failure
• Inflammation of the cornea of the eye
• A hole or sore in the outer layer of the eye (caused by severe inflammation or dry eye syndrome)

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

Side effects may be mild or very serious. Many side effects go away soon after you stop taking erlotinib. In some cases, side effects may be long lasting or may never go away. There also is a risk of death.

**Drugs that interfere with the activity of erlotinib (5/3/05)**

Your study doctor will review your medications and indicate those drugs that might interfere with the absorption of erlotinib, such as drugs that reduce the acid in your stomach, some anti-seizure medications, and some antibiotics. If you are taking erlotinib, always check with your study doctor before starting a new drug.

If you are going to receive erlotinib and you are taking an anti-seizure medication that does interfere with it, you may have to be switched to a different anti-seizure drug. This means that you will not be able to start treatment immediately in order to allow time for changing the medication.

Grapefruit juice can change the level of erlotinib in your blood, so you should avoid grapefruit while taking this drug.

If you are taking drugs to reduce the acid in your stomach, these drugs should be taken at least 4 hours after erlotinib administration.

**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 study doctor immediately. (5/3/05)

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 study doctor immediately. (5/3/05)
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. For women this should continue for at least two weeks after the last dose of drug to ensure that the drug has cleared the body. For men, contraception should continue for three months after the last dose of drug, to ensure that all sperm present in the body during the clinical trial have been replaced. (5/3/05)

Sexual partners of study participants must use adequate birth control measures to prevent pregnancy of a partner.

Ask your study doctor about counseling and more information about preventing pregnancy. (5/3/05)

**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? (5/3/05)**

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 erlotinib 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? (5/3/05)**

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 OSI Pharmaceuticals, Inc. and Schering-Plough Pharmaceutical Companies, and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS? (5/3/05)**

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 erlotinib groups, those drugs will be provided to you free of charge. The Division of Cancer Treatment, and Diagnosis, NCI, will provide you with erlotinib free of charge for this study. Every effort will be made to ensure adequate supplies of erlotinib, 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? (5/3/05)(7/22/08)**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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 http://www.cancer.gov/clinicaltrials or for accurate cancer information including PDQ (Physician Data Query) visit http://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

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

### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
</tr>
<tr>
<td>2</td>
<td>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).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
**APPENDIX III**

**NEUROLOGIC FUNCTION (NF) STATUS**

<table>
<thead>
<tr>
<th>NF</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No neurologic symptoms; fully active at home/work without assistance.</td>
</tr>
<tr>
<td>1</td>
<td>Minor neurologic symptoms; fully active at home/work without assistance.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate neurologic symptoms; fully active at home/work but requires assistance.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate neurologic symptoms; less than fully active at home/work and requires assistance.</td>
</tr>
<tr>
<td>4</td>
<td>Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.</td>
</tr>
</tbody>
</table>
The patient specific supply of temozolomide will be shipped by I.V. Solutions, Inc. only to institutions that have identified a single individual as responsible for receipt and accountability of shipments. Sites must review Section 5.0 of the protocol to assure that all pre-registration requirements have been met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Approved international institutions must submit the SASF 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 SASF must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment. See Section 7.0 under “Drug Ordering and Accountability” for details regarding anticipated shipment and delivery timeframes.
APPENDIX V

STEREOTACTIC RADIOTHERAPY QA GUIDELINES

Below is the direct link to the RTOG Stereotactic Radiotherapy Quality Assurance Guidelines in 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 (5/3/05)

**Drugs that Interfere with Erlotinib Metabolism, i.e., affecting CYP3A4**

<table>
<thead>
<tr>
<th>Inducers CYP3A4</th>
<th>Inhibitors CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Dexamethasone (lowest dose possible)</td>
<td>Anastrozole</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Glucocorticoids (lowest dose possible)</td>
<td>Cannabinoids</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Clotrimazole</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Danazol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Delavirdine</td>
</tr>
<tr>
<td>Primidone</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Diethylthiocarbamate</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Dilazem</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Dirithromycin</td>
</tr>
<tr>
<td>Rofecoxib (mild)</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Entacapone (high dose)</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Ethinyl estradiol</td>
</tr>
<tr>
<td>Griseofulvin (lowest dose possible)</td>
<td>Fluconazole (weak)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Gestodene</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Isoniazid</td>
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<tr>
<td>Phenylbutazone</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Primidone</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Mibefradil</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Miconazole (moderate)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Nefazodone</td>
</tr>
<tr>
<td>Rofecoxib (mild)</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Norfloxacin</td>
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<tr>
<td>Troglitazone</td>
<td>Norfluoxetine</td>
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<tr>
<td>Troglitazone</td>
<td>Omeprazole (weak)</td>
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<td>Valproic acid (weak)</td>
<td>Oxiconazole</td>
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<tr>
<td>Verapamil</td>
<td>Paroxetine (weak)</td>
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<td>Verapamil</td>
<td>Propoxyphene</td>
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<tr>
<td>Zileuton</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Zileuton</td>
<td>Quinine</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Quinupristin and dalfopristin</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Ritonavir</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Saquinavir</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Sertindole</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Sertraline</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Troleandomycin</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Valproic acid (weak)</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Verapamil</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Zafirlukast</td>
</tr>
<tr>
<td><strong>Note:</strong></td>
<td>Zileuton</td>
</tr>
</tbody>
</table>
APPENDIX VIII

Enzyme vs. Non-enzyme Inducing Anti-Seizure Medications

EIAEDs:
- Carbamazepine (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 (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Zonisamide (Zonegran)
- Levetiracetam (Keppra)
- Clonazepam (Klonopin)
- Clonozam (Frisium)