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### Eligibility (See Section 3.0 for details)

- Histopathologically-confirmed glioblastoma multiforme
- The tumor must be supratentorial in location
- Age ≥ 18
- KPS ≥ 60
- No prior radiation therapy to head or neck area, chemotherapy or radiosensitizer
- Absolute neutrophil count ≥ 1500, platelets ≥ 100,000, BUN ≤ 25, Creatinine ≤ 1.5, Bilirubin ≤ 1.5 mg/dL, Hgb ≥ 10 gm, SGPT or SGOT ≤ 2 x normal range
- No malignancy (within the past five years) except non-melanomatous skin cancer or carcinoma *in-situ* of the cervix
- If present, sensory neuropathy must be ≤ grade 1.
- Signed study-specific consent form

### Required Sample Size:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Sample Size</th>
<th>Registration Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>36 (closed 3/22/99)</td>
<td>1/8/99</td>
</tr>
</tbody>
</table>

### Schema

<table>
<thead>
<tr>
<th>Age</th>
<th>(\geq) 18 to &lt; 40</th>
<th>(\geq) 40 to &lt; 60</th>
<th>(\geq) 60</th>
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<tbody>
<tr>
<td>R</td>
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<tr>
<td>E</td>
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<tr>
<td>C</td>
<td>Performance Status</td>
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<tr>
<td>O</td>
<td>KPS ≥ 80</td>
<td>KPS 60-70</td>
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<tr>
<td>D</td>
<td></td>
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</tr>
</tbody>
</table>

60.0 Gy/30 fractions x 2.0 Gy. For the first 46 Gy \((23\ \text{fractions})\) the treatment volume should include the volume of contrast-enhancing lesion and surrounding edema on pre-operative CT/MRI scan plus a 2 centimeter margin. After 46 Gy, the tumor volume should include the contrast-enhancing lesion \((\text{without edema})\) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin.

Thalidomide* will be started on the first day of radiation at a dose of 200 mg p.o. daily, at bedtime. The dose will be escalated every one to two weeks by 100-200 mg daily to a maximum dose of 1200 mg p.o. daily. Continue as long as there is no tumor progression or unacceptable toxicity.

* Patients entered \(\leq\) 3/22/99 were registered to Arm 1 \((\text{thalidomide tablets})\). Patients on Arm 1 will complete their treatment with thalidomide tablets.

Patients registered \(\geq\) 5/4/99 will be registered to Arm 2 \((\text{thalidomide capsules})\).
1. (Y) Does the patient have a histopathologically-confirmed newly diagnosed glioblastoma multiforme with areas of necrosis?

2. (Y) Was the diagnosis made by surgical biopsy or excision and has the patient recovered from the effects of surgery, infection or other complications?

3. (Y) Is the tumor supratentorial in location?

4. (Y) Will therapy begin ≤ 5 weeks after surgery and does the patient have an estimated survival of at least 8 weeks?

5. (N) Has the patient received any previous radiotherapy to the head or neck, chemotherapy, or radiosensitizers?

6. (Y) Is the patient’s KPS ≥ 60 and age ≥ 18?

7. (Y/N) Does the patient have any previous malignancies (except non-melanomatous skin cancers and carcinoma in situ of the uterine cervix or bladder)?

    If yes, has the patient been disease free for ≥ 5 years?

8. (N) Does the patient have a known diagnosis of clinical Acquired Immune Deficiency Syndrome?

9. (Y) Do the patient’s laboratory values meet the criteria outlined in Section 3.1.10?

10. (Y/N) Did the patient have a stereotactic biopsy done for diagnosis?

    If yes, was a preoperative diagnostic contrast-enhanced MRI or CT done?

    If no, were both preoperative and postoperative diagnostic contrast-enhanced MRI or CT done?

11. (Y/N) Is the patient receiving steroids or anticonvulsant medications?

    If yes, has the patient been on stable or decreasing doses for at least two weeks prior to study entry?

12. (Y/NA) If the patient is female and of child-bearing potential, has she had a negative pregnancy test within two days prior to study entry?

13. State reason patient is not being registered to RTOG 93-05.

    1. Not open at institution
    2. Patient not eligible
    3. Patient refused 93-05

(continued on next page)
14. Does the patient have a documented \( \geq \) Grade 2 (CTC version 2.0) sensory neuropathy?

The following questions will be asked at Study Registration:

1. Has the Eligibility Checklist \( (\text{above}) \) been completed?
2. Is the patient eligible for this study?
3. Date the study-specific Consent Form was signed? \( (\text{must be prior to study entry}) \)

__________________________  Patient's Name
__________________________  Verifying Physician
__________________________  Patient ID #
__________________________  Referring Institution # \( (\text{if different}) \)
__________________________  Age
__________________________  Performance Status
__________________________  Birthdate
__________________________  Sex
__________________________  Race
__________________________  Social Security Number
__________________________  Zip Code \( (9 \text{ digit if available}) \)
__________________________  Method of Payment
__________________________  Will any component of the patient’s care be given at a military or VA facility?
__________________________  Treatment Start Date
__________________________  Treatment Assignment

Completed by _______________________________  Date __________________________
1.0 INTRODUCTION

1.1 Background

The diagnosis of malignant glioma includes tumors characterized as astrocytoma with anaplastic foci (AAF) or as glioblastoma multiforme (GBM). Despite important advances in diagnosis and therapy, malignant gliomas continue to frustrate clinical investigators in their tendency to recur and progress at or near their original location. A number of studies performed by the Brain Tumor Study/Cooperative Group (BTSG or BTCG) and the Radiation Therapy Oncology Group (RTOG) have settled several important therapeutic issues regarding malignant gliomas. At the same time these studies have raised several new questions, particular the role of chemotherapy in the overall management of patients with glioblastoma multiforme. The major issue in the treatment of glioblastoma pertinent to this study is the role of thalidomide in improving time to tumor progression and survival.

1.2 Prior Studies

Two successive randomized BTSG studies, 69-01 and 72-01 demonstrated superior survival for patients with malignant glioma receiving whole brain RT to 60 Gy in single 1.8 to 2.0 Gy daily fractions with or without BCNU (69-01) or CCNU (72-01) as compared to either drug alone or to supportive care following biopsy or subtotal resection. An evaluation of these trials as well as BTSG 66-01 by Walker, et al. suggested that an RT dose response existed to at least 60 Gy, with an increase in median survival time observed from 28 to 42 weeks. A report from the randomized trial BTCG 80-01 demonstrated that at least the final portion of the 60 Gy can be delivered via a "coned-down" field including the primary tumor plus a margin without compromise on outcome.

In RTOG 74-01 no survival difference was observed between the treatment arm using 60 Gy whole brain RT plus a 10 Gy "boost" and the treatment arm using 60 Gy whole brain without a boost. The advent of improved neuroradiologic techniques, especially computed tomography and magnetic resonance imaging, in two RTOG malignant glioma studies (83-02 and 86-12) have replaced whole brain RT with a large partial brain field encompassing the primary tumor and surrounding edema with margin followed by a smaller field to the tumor plus margin. This approach has the advantage of decreasing the volume of neural tissue irradiated and thereby decreasing treatment toxicity, without compromising tumor control. Based on these studies, current standard radiotherapeutic management of malignant gliomas involves delivery of 60 Gy in 1.8 to 2.0 Gy single daily fractions using the shrinking field technique described above. Two reports correlated the location of tumor failure of glioblastoma multiforme with pretreatment tumor and edema volumes and one of these reports observed tumor infiltration within and just beyond the peritumoral edema, confirming the need for adequate radiotherapeutic coverage of this region.

1.3 Role of Chemotherapy and Biological Response Modifiers for Malignant Glioma

Several RTOG and BTSG/BTCG studies have confirmed that the nitrosourea carmustine (1,3-bis (2-chloroethyl)-1 nitrosourea, i.e., BCNU) confers a real but modest survival benefit to the advantage seen with RT alone in at least several patient categories. In BTSG 69-01, patients receiving BCNU + RT had an improved survival rate at 18 months compared to RT alone. While no overall survival difference was observed in RTOG 74-01 between the RT/BCNU arm and RT alone, a survival difference (p < 0.01) was observed in patients less than 60 years of age in favor of the RT/BCNU arm (median survival: 12.0 vs. 8.7 mo.).

Both cooperative groups have studied other systemic agents to improve on the modest benefit seen with BCNU. No further survival advantage was seen with MeCCNU (BTSG 72-01), MeCCNU plus dacarbazine (RTOG 74-01), methylprednisone (BTSG 75-01), misonidazole (RTOG 79-18 and BTCG 77-02), streptozotocin (BTCG 77-02), and procarbazine, hydroxyurea, and VM-26 (BTCG 80-01). In a Northern California Oncology Group study comparing post-RT BCNU versus procarbazine, CCNU, and Vincristine, (PCV), Levin et al. reported an improved survival among "adequately treated" anaplastic glioma patients treated with PCV over BCNU. This difference was less apparent when all randomized patients with anaplastic gliomas were analyzed and was not present among patients with GBM, the histology seen among 80-85% of patients enrolled on RTOG glioma trials.

Other strategies have included: (1) high dose preirradiation chemotherapy; (2) intra-arterial (IA) chemotherapy; and (3) new systemic agents. The preirradiation chemotherapy regimens have included high dose BCNU with autologous bone marrow transplantation, "eight-drugs-in-one-day" chemotherapy, and infusional BCNU and cisplatin. Despite responses, no improvement in median survival time over
conventional therapy has been suggested by these pilot studies. IA chemotherapy offers the theoretical advantage of enhanced drug delivery to the tumor site while minimizing systemic side effects. While Mahaley, et al. reported a 34% response rate among recurrent irradiated gliomas using nonstandard response criteria, most investigators, including the Southwest Oncology Group, have reported unacceptable toxicity and lack of improved efficacy for IA versus intravenous chemotherapy.

1.4 Angiogenesis and Thalidomide

Angiogenesis or vascular proliferation is one of the four major pathologic factors for malignant gliomas. Over-expression of VEGF, bFGF, TGF-, and PDGF has been identified in malignant astrocytomas, while down regulation of thrombospondin, an angiogenesis inhibitor, and has also been identified. These are apparent mechanisms that malignant gliomas utilize to regulate the degree of neovascularization during malignant progression.

Thalidomide was developed in the 1950's as a sedative that in rodent models was so nontoxic that a LD50 could not be established. Unfortunately, thalidomide turned out to be a potent teratogen in humans, causing dysmelia in babies born to mothers who had taken the drug during pregnancy. There has been renewed interest in the drug since the observation in 1994 by D. Amato and co-workers that thalidomide has potent anti-angiogenic properties.

Thalidomide is a potentially promising anti-angiogenic agent for the treatment of cancer based on the fact that it is an oral agent with minimal toxicity, thereby, potentially allowing long term, chronic maintenance therapy. A phase II trial of thalidomide was performed in patients with recurrent high-grade astrocytomas. Each patient received thalidomide starting at a dose of 800 mg per day and escalating to a total dose of 1200 mg per day. A total of 39 patients were treated in this trial. In general, the drug was well tolerated with the only major adverse events being seizures in 4 patients, all of whom either had seizures prior to taking thalidomide, or had rapidly progressive tumor. An additional 2 patients had neurocortical somnolence that was rapidly reversible following lowering of the thalidomide dose by 50%. Although response data is still being compiled, of 32 evaluable patients, at least 4 patients had objective radiographic regressions on MRI scans lasting between 2 and 9 months, and another 12 patients had stabilization of disease for at least 2 months. Thus, it appears that thalidomide does have some biologic activity against gliomas.

In the laboratory, thalidomide appeared to work by inhibiting the angiogenic activity of bFGF, which presumably may only account for neovascularization. A large recurrent tumor has a large number of established vessels already, thus rendering the activity of thalidomide less apparent. The best time for applying thalidomide inducing angiogenesis activity may well be at the time of least tumor burden, after maximal tumor reduction and radiation therapy. Using this strategy, thalidomide will function as a maintenance agent to prevent tumor progression resulting from neovascular formation.

1.5 Quantification of Tumor Angiogenesis

Quantification of tumor angiogenesis or microvessel density (MVD) is possible. The MVD is a quantitative measurement of the number of small blood vessels within a given area of tissue on a histological slide. The neovascularity can readily be identified by immunohistochemistry in formalin-fixed paraffin-embedded tissue using an antibody to human von Willebrand factor (factor VIII-related antigen) or another antigen present on endothelial cells (CD31 and CD 34). An association of tumor extent/aggressiveness and decreased patient survival has been observed in studies of patients with cancers of the bladder, brain, breast, cervix, endometrium, gastric, head and neck, lung, ovary, rectum, testis, and prostate.

1.6 Relevance of Project

The upregulation of angiogenesis is a key event that accompanies glioma progression. Low-grade gliomas are moderately vascularized tumors whereas high-grade gliomas show prominent microvascular proliferation and areas of high vascular density.

Brain tumors, especially glioblastoma multiforme, have significant angiogenic activity primarily by the expression of the angiogenic factor VEGF, Platelet-derived endothelial cell growth factor (PD-ECGF), and basic FGF. All of have all been recently immunohistochemically localized in human gliomas.
Vascular pathology is a key feature of glioblastoma multiforme characterized by hypervascularity, vascular permeability, and hypercoagulability.

Work by Assimakopoulou and colleagues\(^4\) have shown that astrocytic tumors, particularly malignant astrocytomas (grade III, IV), were highly vascular. The mean MVD as regards the supratentorial astrocytic neoplasms was 14.5 in astrocytomas (grade I/II), 42.3 in anaplastic astrocytomas (grade III) and 50.2 in glioblastomas (grade IV).

Fibroblast growth factors (FGFs) share 30-55% sequence identity and similar gene structure and are capable of inducing transformation via an autocrine mechanism when introduced into cells expressing the appropriate FGF receptor. Acidic FGF (also designated aFGF or FGF1) and basic FGF (bFGF or FGF-2), prototypes of this expanding family of growth regulatory molecules, are well known for their ability to stimulate the proliferation of cells of mesenchymal, epithelial and neuroectodermal origin. In the human brain the levels and subcellular localization of FGF-2 differ between quiescent and reactive astrocytes. Quiescent cells express a low level of FGF-2, which is located predominantly within the cytoplasm. In reactive astrocytes, the expression of FGF-2 increases and the proteins are found in both the cytoplasm and nucleus. In glioma tumors, FGF-2 is overexpressed in the nuclei of neoplastic cells.\(^5\)

To date, there has been no clinical trial that has attempted to prospectively or retrospectively evaluate awMVD and clinical response to an anti-angiogenic agent. The proposed study will evaluate the feasibility of awMVD evaluation and examine its potential for obtaining predictive information with phase 2 clinical outcome data in patients treated with thalidomide and radiation therapy. We will also evaluate the expression of one protocol target for thalidomide, namely, basic FGF (bFGF/FGF-2).

The study will use several newly developed advanced enhancements for awMVD to control subjectivity and obtain accurate results. Calculations of optimized awMVD values will be largely free of the variability of human readers, and are insensitive to other variables such as slide orientation in the optical field or the time interval between repeated measurements on the same image source. It is hoped that the final result will be a stable, reliable determination that repeatable processing to determine optimized awMVD values.

1.7 **Immunohistochemistry for Basic Fibroblast Growth Factor-2 Antigen**

Immunohistochemical staining will be performed using the avidin-biotin-peroxidase staining complex (ABC) method as described above. Slides will be incubated with polyclonal goat IgG, to FGF-2 (Santa Cruz Biotechnology, Santa Cruz, CA).

2.0 **OBJECTIVES**

2.1 To determine if thalidomide given orally once daily starting with conventional RT can improve the median survival time and time to progression of adults with supratentorial glioblastoma.

2.2 To evaluate the toxicity of conventional RT and thalidomide given in this manner.

2.3 The present proposal is designed to evaluate the prognostic ability of optimized area weighted microvessel density to stratify patients with high-grade gliomas who will receive thalidomide and radiation therapy.

2.3.1 Evaluate the degree of angiogenesis by determination of optimized area weighted microvessel density (awMVD) of brain tumor biopsy and resection specimens (primary and metastasis).

2.3.2 Investigate tumor vascularization (MVD) to examine its potential for obtaining predictive information with phase 2 clinical outcome data in patients treated with thalidomide and Radiation Therapy on RTOG trial 98-06.

2.3.3 Evaluate level of basic fibroblast growth factor-2 (bFGF/FGF-2). Known to be overexpressed in the nuclei of gliomas, and whose angiogenic activity is inhibited by thalidomide.

3.0 **PATIENT SELECTION**

3.1 **Conditions for Patient Eligibility**

3.1.1 Histopathologically-confirmed newly diagnosed glioblastoma multiforme (with areas of necrosis).

3.1.2 Diagnosis must be made by surgical biopsy or excision.

3.1.3 The tumor must be supratentorial in location.

3.1.4 The patient must have recovered from the effects of surgery, or post-operative infection and other complications before entry into the study.

3.1.5 Therapy must begin ≤ five weeks after surgery.
3.1.6 Patients must have an estimated survival of at least 8 weeks.

3.1.7 Karnofsky Performance Status of \( \geq 60 \).

3.1.8 Age \( \geq 18 \).

3.1.9 A diagnostic contrast-enhanced MRI or CT scan must be performed preoperatively and postoperatively prior to the initiation of radiotherapy.

3.1.9.1 Patients diagnosed only by stereotactic biopsy do not require the post-op scan.

3.1.10 Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 10 grams, and the hematocrit is less than 30%, then correction by transfusion is indicated before entry into the study.

\[ \text{Hematologic:} \quad \text{Hemoglobin} \geq 10 \text{ grams} \]
\[ \text{Absolute neutrophil count} \geq 1500 \text{ (ANC) per mm}^3 \]
\[ \text{Platelets} \geq 100,000 \text{ per mm}^3 \]

\[ \text{Renal:} \quad \text{BUN} \leq 25 \text{ mg} \]
\[ \text{Creatinine} \leq 1.5 \text{ mg} \]

\[ \text{Hepatic:} \quad \text{Bilirubin} < 1.5 \text{ mg/dL} \]
\[ \text{SGPT or SGOT} \leq \text{twice normal range} \]

3.1.11 Patients receiving steroids or anti-seizure medications should be on stable or decreasing doses for at least two weeks prior to entry. The use of phenobarbitol should be avoided since it may cause the patient to become oversedated.

3.1.12 Patients must not be pregnant or nursing, and all patients (both men and women) must be willing to practice birth control during, and for 2 months after, treatment with thalidomide. Thalidomide may interfere with hormonal-based contraception; therefore, barrier methods of contraception (i.e. diaphragm, condom) must be used rather than birth control pills alone. See Section 11.2.4.

3.1.13 The patient must give written study-specific informed consent. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

3.2 Conditions for Patient Ineligibility (1/8/99)

3.2.1 Gliomas graded less than glioblastoma multiforme.

3.2.2 Recurrent malignant gliomas.

3.2.3 Patients in whom metastases are detected below the tentorium or beyond the cranial vault.

3.2.4 Major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of the protocol therapy.

3.2.5 Previous radiotherapy to the head or neck.

3.2.6 Previous malignancies, except for non-melanomatous skin cancers and carcinoma in situ of the uterine cervix or bladder, unless disease-free for \( \geq 5 \) years.

3.2.7 Prior chemotherapy or radiosensitizer.

3.2.8 Patients who cannot be regularly followed by the investigator.

3.2.9 Patients with known diagnosis of clinical Acquired Immune Deficiency (AIDS).

3.2.10 Grade \( \geq 2 \) sensory neuropathy based on the NCI Common Toxicity Criteria (Version 2.0).

3.2.11 Patients who are eligible for RTOG 93-05 unless patient has refused RTOG 93-05 or the study is not open at your institution.

4.0 PRETREATMENT EVALUATION

4.1 Mandatory Studies (within 14 days prior to registration)

4.1.1 Complete history and general physical examination.

4.1.2 Detailed neurological examination immediately prior to beginning protocol treatment.

4.1.3 Steroid and anticonvulsant doses must be documented.

4.1.4 CBC with differential, platelet count, blood chemistries (Total protein, albumin, calcium, phosphorus, glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, and SGPT).

4.1.5 Gd-MRI or CT with contrast performed preoperatively and postoperatively prior to the initiation of radiotherapy (mandatory for eligibility) within 21 days prior to registration. The postoperative scan is not required if the patient was diagnosed by stereotactic biopsy.

4.1.6 Serum pregnancy test within two days of study entry.

4.1.7 The Mini-Mental Status Exam will be administered prior to the start of protocol treatment.

5.0 REGISTRATION PROCEDURES
5.1 Patients can be registered only after pretreatment evaluation is completed and 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 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY PARAMETERS

6.1 Dose Definition and Schedule

Radiotherapy must begin within 5 weeks of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over six weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose that shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
6.1.2 For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.
6.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
6.1.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
6.1.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However if this technique is utilized the dose shall be specified at the center of the target volume.
6.1.6 Other or complex treatment arrangements: at the center of the target volume.

6.2 Physical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from Cobalt 60 up to and including 10 MV photons. Selection of the appropriate photon energy (ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy ≤ 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines secondary collimation is required. Electron, particle or implant boost is not permissible.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. This initial target volume shall include the contrast-enhancing lesion and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0 centimeter margin. If no surrounding edema is present, the initial target volume should include the contrast enhancing lesion plus a 2.5 centimeter margin. The initial target volume will be treated to 46.0 Gy in 23 fractions. After 46 Gy, the tumor volume for the conedown treatment should include the contrast-enhancing lesion (without edema) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin.

6.4 Treatment Planning

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores at Headquarters reviews. Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity within the target volume shall be kept to ≤ 10%.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. The use of vertex fields requires either a diagram or photograph of treatment position to be submitted to RTOG Headquarters.

6.5 Dose Limitation to Critical Structures
The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 60.00 Gy, the retina of at least one eye (*but preferably both*) to 50.00 Gy, and the brain stem to 60.00 Gy. When the optic chiasm must be included in the full dose, then there may be a finite unknown risk of developing blindness.

6.6 **Documentation Requirements**

A copy of the pretreatment CT/MRI, the treatment prescription form, treatment calculation form, simulation films and representative portal films of each initial field must be forwarded to RTOG Headquarters according to Section 12.1. At the completion of treatment, the following shall also be forwarded to Headquarters: daily treatment record, all isodose distributions, simulation and portal films of the reduced fields, and the radiotherapy summary.

6.7 **Acute Radiation Toxicities (3/24/10)**

6.7.1 Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.

6.7.2 Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation.

6.7.3 Hematologic toxicities should be rated on a scale of 0-5 as defined in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) **beginning April 1, 2010**. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

7.0 **DRUG THERAPY**

7.1 **Thalidomide (NSC# 66847) (5/4/99)**

7.1.1 *Other Name*

Thalomid™

7.1.2 *Molecular Formula*

\[C_{13}O_4N_2H_9\] (M.W. 243)

7.1.3 *Description*

Thalidomide is a racemate

7.1.4 *How Supplied*

Supplied by CTEP as 50 mg hard gelatin capsules

7.1.5 *Storage*

Thalidomide should be stored at room temperature

7.1.6 *Route of Administration*

Oral

7.1.7 *Toxicities*

Drowsiness and sedation, headache, constipation, nausea, dryness of mucosa, erythematous skin eruptions, peripheral neuropathy, increased appetite, weight gain, loss of libido, edema of face and extremities, galactorrhea, dry skin, leukopenia, menstrual abnormalities, pruritis, alopecia, eosinophilia, somnolence, depression and of course, teratogenic effects.

7.1.8 **WARNING**

There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking thalidomide even for short periods. Therefore, this teratogenic action of thalidomide necessitates:

7.1.8.1 Female patients having any chance of becoming pregnant must have a pregnancy test performed within 24 hours of beginning thalidomide, weekly for the first 4 weeks of treatment, and then every 4 weeks if the patients periods are regular or every 2 weeks if they are not.

7.1.8.2 Female patients must either abstain from all reproductive sexual intercourse or use 2 methods of birth control at least 1 highly active method (*e.g. intrauterine device [IUD], hormonal [birth control pills, injections, or implants], tubal ligation, or partner’s vasectomy*) and 1 additional effective method (*e.g. latex condom, diaphragm, or cervical cap*) at 4 weeks before starting thalidomide therapy, during therapy, and for 4 weeks after discontinuing thalidomide therapy even when there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal or has had no menses for at least 24 consecutive months.

7.1.8.3 Male patients must be counseled about the possibility that thalidomide may be present in semen. Men must use a latex condom every time they have sexual intercourse with a woman during therapy and for 4 weeks after discontinuing thalidomide, even if they have had a successful vasectomy.
7.1.8.4 The bottle label will bear:

“Warning: This product is contraindicated in men and women of childbearing age. Thalidomide is an investigational new drug that can only be prescribed by a physician.”

7.1.8.5 If secondary re-packaging is necessary then all bottles should bear a warning similar to the following:

“Thalidomide must not be used by males and females who are sexually active.”

7.1.8.6 In addition, all bottles should have affixed a warning label similar to the following:

“This medication may cause drowsiness, alcohol may intensify this effect. Use caution when driving or operating machinery.”

7.2 Schedule (5/4/99)

Beginning first day of radiation therapy, patients will be started on thalidomide 200 mg at bedtime every night. The dose will be escalated by 100-200 mg every 1-2 weeks, dependent on the level of sedation, until a final dose of 1200 mg per day is attained. Eight weeks of treatment will be considered as one course. Thalidomide will be given continuously as long as there is no tumor progression or unacceptable toxicity.

7.3 Dose Adjustment (3/24/10)

Initially, sedation and lethargy will be the major dose limiting factor. During the dose escalation phase, patients will be seen in 1-2 week intervals. The dose will be increased or decreased by 100-200 mg depending on the level of sedation and lethargy (grade 3 or less). When grade 3 or higher hematological or non-hematological toxicity is observed, treatment with thalidomide will be withheld. Treatment will be resumed at a 25% dose reduction when the toxicity has resolved to grade 2 or lower. If the patient does not have a toxicity greater than grade 1 at the reduced dose for a period of 6 weeks, the dose may be returned to the previous dose. For patients in whom grade 3 or higher toxicity does not resolve to grade 2 or lower within 4 weeks, thalidomide will be discontinued permanently. Patients who have another grade 3 or higher toxicity at the reduced dose can have another 25% dose reduction when the toxicity has resolved to grade 2 or lower. For peripheral neuropathy, grade 2 or higher will be considered dose limiting toxicity requiring dose reduction as described above.

7.4 Steroid Doses

All patients should be maintained on the lowest steroid dose necessary for neurological stability.

7.5 Efficacy of Treatment

All patients, regardless of the dose, will be considered evaluable for efficacy toxicity. Any patient who progresses clinically during the first 8 weeks of therapy will be evaluated by CT/MRI scan and will be considered a protocol failure if disease progression is confirmed by imaging.

7.6 Accountability and Supply (5/4/99)

7.6.1 The Principal Investigator (or authorized designee) at each participating institution may request thalidomide, from NCI’s Pharmaceutical Management Branch (PMB). PMB policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of 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. 707, Bethesda, MD 20892. Specify tablets or capsules. See Sections 7.6.2 and 7.6.3.

7.6.2 Patients entered ≤ 3/22/99 were registered to Arm 1 (thalidomide tablets). Patients on Arm 1 will complete treatment with thalidomide tablets.

7.6.3 Patients entered ≥ 5/4/99 will be registered to Arm 2 (thalidomide capsules).

7.7 Drug Inventory Records

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD, using the NCI Drug Accountability Record Form (see the NCI Investigators Handbook for Procedures for Drug Accountability and Storage).

7.8 Adverse Drug Reaction Reporting

7.8.1 This study will utilize CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for toxicity and Adverse Event reporting beginning April 1, 2010. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE. See Appendix IV for protocol reporting guidelines.

7.8.2 This study will be monitored by the Clinical Data Update System (CDUS) version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.
### 7.8.3 Reporting

<table>
<thead>
<tr>
<th>Unknown Reaction</th>
<th>Known Reaction</th>
</tr>
</thead>
</table>
| Grades 2-3 *(Note 2)*  
Written report to follow within 10 working days *(Note 3).* | Grades 4 and 5  
Report by phone to IDB within 24 hrs *(Note 1)*  
Written report to follow within 10 working days *(Note 3).* |
| Grades 4 and 5  
Not to be reported as ADRs. These toxicities should be submitted as part of study results. | Grades 4 and 5  
Written report to follow within 10 working days *(Note 3).* |
| Grade 4  
Myelosuppression not to be reported, but should be submitted as part of study results. | Grade 5  
Aplasia in Leukemia patients-written report within 10 working days. |

Note 1: Telephone number available 24 hours daily: (301) 230-2330 *(Recorder after hours).*

Note 2: See the DCTD/CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTEP Active Version of the CTCAE will be utilized for AE reporting **beginning April 1, 2010**. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

Note 3: Report to: *Investigational Drug Branch, Post Office Box 30012, Bethesda, Maryland 20824.*

Note 4: A list of all known toxicities can be found in the protocol document or consent form.

Note 5: **Reactions judged definitely not treatment-related should not be reported.** However, a report should be submitted if there is reasonable suspicion of drug effect.

### 7.8.4 Pregnancy

The NCI and RTOG must be notified immediately if any patient becomes pregnant while taking thalidomide.

### 7.9 Clinical Trials Agreement (1/8/99)

The agent(s) *(hereinafter referred to as “Agent[s]”)*, used in this protocol is/are provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between *Company (or Companies) (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 or CRADAs, 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 or CRADA 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 718
Bethesda, Maryland 20892
FAX (301) 402-1584

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

8.0 SURGERY

The extent of surgical resection prior to protocol entry shall be documented as a) biopsy, b) subtotal resection, or c) total resection as described by the operative report and/or postoperative imaging.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 LABORATORY CORRELATES (5/4/99)

10.1 Immunoassay for bFGF/VEGF Level

10 ml of blood will be collected at three different time points: before radiation and thalidomide is started, at three months, and at six months after initiation of therapy. Serum will be separated, frozen and stored until requested by Dr. Yung. Serum level of bFGF and VEGF will be assayed by ELISA assay kits from R&D.

10.1.1 Ten ml of blood should be drawn at specified time points (see Section 11.1) in a red top tube. Remove serum after blood is clotted. Freeze serum at -80°C. Label each tube with patient ID, study and case numbers, and specify at which time point the blood was drawn. Store serum at your facility until requested by the study chair. Note: -80°C freezer is preferable, although -20°C freezer (noncycling) is acceptable.

10.2 Immunostain for bFGF/VEGF

Protein expression of bFGF and VEGF will be determined by standard immunohistochemistry staining techniques with monochrome antibody against bFGF and VEGF. A semi-quantitative scale of 1+ to 4+ will be used to determine the expression level. The results will be correlated with response to therapy.

10.3 RTOG Tissue Bank

10.3.1 Patients entered on this study must submit materials to the RTOG Tissue Bank for the laboratory correlative studies.

10.3.2 The following must be provided:
10.3.2.1 A paraffin-embedded tissue block of the tumor obtained at surgical resection or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.3.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.3.2.3 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.3.3 RTOG will reimburse pathologists from submitting institutions $100. per case if proper materials are submitted (reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement).

10.3.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).

10.3.5 Materials will be sent to:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143
(801) 321-1929
FAX (801) 321-5020

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (5/4/99)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Prestudy</th>
<th>During XRT</th>
<th>During Thalidomide</th>
<th>Post Thalidomide</th>
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<tbody>
<tr>
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<tr>
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<td>x^f</td>
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</tr>
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<td>Blood Chemistries</td>
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<td>Serum bHCG, pregnancy test</td>
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<td>Mini Mental Status Exam</td>
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<td>x^d</td>
<td></td>
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<tr>
<td>Toxicity Evaluation</td>
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<tr>
<td>Followup Evaluation</td>
<td></td>
<td></td>
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<td>x</td>
</tr>
<tr>
<td>Laboratory Correlates (See Section 10.1)</td>
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<td></td>
<td></td>
<td>x^g</td>
</tr>
</tbody>
</table>

a. Weekly during XRT; every 2 weeks during dose escalation or reduction, then q 8 weeks
b. Every 2 months during protocol treatment, then at the time of neurologic deterioration. See Section 11.2.3.
c. As applicable for women of childbearing potential. See Section 11.2.4.
d. Submit with every followup form (F1).
e. Every 8 weeks.
f. Every 2 weeks during thalidomide dose adjustment.
g. Blood is drawn at 3 time points: 1) before radiation and thalidomide, 2) at 3 months, and 3) at 6 months after initiation of therapy.

Note: It is preferable that patients are followed with the same radiological study (Gd-MRI vs. Contrast CT) as the baseline study.

11.2 Evaluation During Study:
11.2.1 A neurologic examination shall be performed once a week during radiation therapy, every two weeks during thalidomide escalation or reduction and every two months during thalidomide therapy.

11.2.2 Skin within the treatment portal shall be examined at least once per week during radiation therapy.

11.2.3 The Gd-MRI/contrast CT of the brain shall be obtained prior to radiotherapy, every 2 months during therapy, and at the time of neurologic deterioration. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation. (5/4/99)

11.2.4 Within 24 hours prior to starting thalidomide, all female patients of childbearing potential must have a negative serum bHCG pregnancy test. In addition, patients should have a pregnancy test every week for four weeks after the initial dose of thalidomide. The FDA recommends monthly pregnancy tests while receiving treatment as long as menstrual periods are normal, and every two weeks if menstrual periods are irregular. Female patients of childbearing potential should use two simultaneous methods of contraception. Pregnancy testing should be done four weeks after the last dose of thalidomide and for at least one month after the last dose of thalidomide. (5/4/99)

11.2.5 While a patient is receiving thalidomide, blood counts are required every two weeks. Serum chemistries will be obtained every 8 weeks during treatment.

11.3 MRI/CT Review
The serial MRI/CT scans shall be examined at the institution by an independent reviewer, a neuroradiologist. The evaluation of the scans will be compared to and correlated with the patient's clinical course.

11.4 Overall Response
11.4.1 Complete Response (CR): shall be defined as the circumstance when the tumor is no longer seen by neuroimaging provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.4.2 Partial Response (PR): Decrease of ≥50% in the product of two diameters provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.4.3 Minor Response (MR): Decrease in diameter products of < 50% provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.4.4 Stable Disease (SD): shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids.

11.4.5 Progression (P): shall be defined as a > 25% increase in tumor area (two diameters) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation at this point.

11.5 Criteria for Evaluation of Therapy Effectiveness
11.5.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and MRI/CT scans may provide a guide to the actual course. Time interval to progression will be measured from the first day of treatment until deterioration is documented by the individual Investigator using these guides. The patient should preferably be followed with the same diagnostic imaging study (CT or MRI).

11.5.2 Overall survival will be measured from the time of first surgery until death.

11.5.3 Post mortem examination of the cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on malignant and normal brain tissue.

11.5.4 Patients will be removed from followup for the following reasons: not complying with Section 3.0 or refusal to take thalidomide. These patients will be excluded from the analysis.

12.0 DATA COLLECTION
12.1 Summary of Data Submission (5/4/99)
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

Data When Due
Demographic Form (A5) Within two weeks of registration
On-study Form (I1)

Pretreatment CT/MRI scan (both pre- and...
post-surgery) (C1) and reports (C3)
Pathology Report (P1)
Pathology Blocks/Slides (P2)
Baseline Mini-Mental Exam (MS)
Radiotherapy prescription (T2)
Preliminary Dosimetry Information:
Simulation & Portal Localization films (T3)
Central axis calculations (T4)
Radiotherapy Form (T1)
Final Dosimetry Information:
Daily treatment record (T5)
Isodoses (T6)
Simulation & Port films of all fields (T8)
Study Specific Flow Sheet (SF)
Initial Followup Form (FS)
Followup Mini-Mental Exam (MS)
Follow-up Form (F1)
Post-treatment MRI/CT (C2)
and report (C3)
Operative reports (S2), surgical reports (S5)
(for subsequent surgery)
Autopsy Report (D3)

12.2 CT/MRI Documentation (5/4/99)
The contrast-enhanced MRI/CT taken before surgery and after-surgery-before-radiotherapy begins must be submitted within two weeks of registration. A post-RT scan must also be submitted to Headquarters. A MRI/CT must be done at the time of neurologic deterioration, suggestive of tumor recurrence and not related to lowered steroid dose, unless the last MRI/CT had been done within one month and was compatible with recurrence. The patient should consistently be followed with the same diagnostic study. Subsequent scans and reports, other than the pre-entry and post-RT scans, should be forwarded to RTOG Headquarters only in the event of a suspected grade ≥ 3 RT toxicity.

13.0 STATISTICAL CONSIDERATIONS (5/4/99)
13.1 Study Endpoints
13.1.1 Overall survival
13.1.2 Acute and late toxicities associated with thalidomide and radiotherapy
13.1.3 Time to progression
13.2 Sample Size
The primary objective of this study is to estimate the median survival time (MST) for glioblastoma multiforme (GBM) patients treated with thalidomide and radiotherapy. Patients enrolled onto this trial should not be eligible for RTOG 93-05; thus, the majority of patients will have a maximum tumor diameter greater than 4.0 cm. Historically, GBM patients with RPA class of III and IV have an estimated MST of 12.7 months. A sample size of 60 evaluable class III and IV patients followed over 18 months will ensure at least 80% probability of detecting a minimum of 35% improvement in MST compared to the RTOG
glioma database at the 0.20 significance level (one-sided). Based on previous RTOG GBM studies, 75% of patients are predicted to be in class III and IV, resulting in an overall sample size of 80 evaluable patients in order to accrue 60 class III and IV patients. Furthermore, assuming a 5% ineligibility/inevaluableity rate, the total sample size required for Arm 2 will be **84 patients**.

13.3 **Inclusion of Women and Minorities**

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender. The RTOG found no difference in survival of glioblastoma multiforme patients by race. Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, 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.

13.4 **Patient Accrual**

The patient accrual is projected to be 14 cases per month, based upon the monthly accrual for RTOG 90-06. At this rate, it will take six months to reach the required total accrual of 84 cases. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.5 **Suspension of Accrual Due to Morbidity**

If there is any fatal treatment morbidity, the accrual will be suspended, and all data pertaining to the event will be reviewed by the study chairman and reported to the RTOG Data Monitoring Committee (DMC) for review.

13.6 **Analyses Plans**

13.6.1 **Interim Analyses**

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;

b) the quality of submitted data with respect to timeliness, completeness, and accuracy;

c) the frequency and severity of the toxicities.

Through examining the above items, the RTOG DMC and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study, and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.6.2 **Analysis for Reporting the Initial Treatment Results**

This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. The usual components of this analysis are:

a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;

b) reporting of institutional accrual;

c) distribution of important prognostic baseline variables – (age, KPS, neurologic function, extent of surgery, time from first symptom, location of primary, and site of tumor);

d) observed results with respect to the endpoints described in Section 13.1.

The estimated median survival from this sample will be tested against the historical control presented in Section 13.2 using a one-sample test. Median survival estimates will also be calculated for patient subgroups according to the subgroups identified in Curran et al. The Brookmeyer-Crowley confidence interval for median survival will be provided for all estimates.

An improvement in MST of at least 35% dependent upon appropriately identified baseline comparison will be encouraging for further study.
REFERENCES


44. Collin, O. and Bergh, A.  Leydig cells secrete factors which increase vascular permeability and endothelial cell proliferation.  International Journal of Andrology.  19:221-228;  1996.


RESEARCH STUDY

I have the right to know about the procedures that are used in clinical research so I can decide whether to undergo the procedure after knowing the risks, benefits, and alternatives involved. This is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I have been diagnosed with a brain tumor called a glioblastoma multiforme. Further treatment is recommended. The usual treatment in cases such as mine is radiation therapy plus chemotherapy or biological therapy. In this study, radiation therapy will be followed with the drug thalidomide to attempt to improve the effectiveness of the radiation. This study will also gather information about the potential benefit of thalidomide.

DESCRIPTION OF PROCEDURES

This study involves a once day radiation treatments to the tumor. Radiation treatments will be given five times a week (Monday to Friday) for six weeks. When I begin radiation treatment, I will also begin taking four thalidomide capsules (by mouth) every evening at bedtime. The number of capsules will increase by 2-4 capsules every week or two to a maximum of 24 capsules a night provided I do not have any serious side effects as described by my doctor. Every 8 weeks, a repeat MRI or CT scan will be done. I will return to my doctor for exams to evaluate the tumor and effects of treatment.

If I am female and physically able to have children: (1) I must not be pregnant or be nursing a child; (2) I must refrain from activities intended to result in pregnancy (e.g. fertilization methods); and (3) I must abstain from reproductive sexual intercourse, or use two highly effective birth control methods at the same time while receiving thalidomide and for one month after the last dose of thalidomide.

If I am a male who has not had a vasectomy, I must abstain from reproductive sexual intercourse until one month after the last dose of thalidomide.

The Division of Cancer Treatment and Diagnosis, National Cancer Institute will provide thalidomide free of charge for this study. Thalidomide is not approved for general sale in the United States. Thalidomide is being used in an investigational manner in this study.

Also, at the time of my diagnosis by biopsy, all or some of my tumor was removed. As is usually done, this tissue went to the hospital’s pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor samples and a small sample of my blood for additional tests. Since this tissue was removed at the time of surgery or biopsy, my permission to use this tissue will not lead to any additional procedures or expense. This tissue may be sent to a central office for review and research investigation associated with this protocol.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Risks from Radiation Therapy: include some or all of the following side effects: scalp redness or soreness, hair loss, which may be temporary or permanent, dry mouth or altered taste, hearing impairment, fatigue, sleepiness or temporary aggravation of tumor symptoms such as headaches, seizure, or weakness. There is a risk of injury to the eyes from radiation therapy with the possibility of blindness. Radiation sometimes causes late side effects such as mental slowing or behavioral change.
Occasionally radiation causes severe local damage to normal brain tissue, a condition called necrosis. Radiation necrosis can mimic recurrent brain tumor or those of a stroke and may require surgery.

**Risks from Thalidomide:** Thalidomide was first used in the 1950’s for morning sickness during pregnancy and as a sleeping pill until it was discovered that it caused severe birth defects. The most common side effect of the drug is drowsiness. Because of this, I must not drive while taking thalidomide. The sleepiness will stop when I stop taking thalidomide. Other common side effects are headache, constipation and numbness, tingling, or pain in my hands or feet. These side effects can be very troublesome for me. In most cases, these side effects stop when the drug is stopped. In some cases, the numbness may become permanent if the thalidomide is continued. My doctor will provide me with information to help relieve the constipation.

Other side effects may include increased appetite, weight gain, low sex drive, nausea, skin rash, itchiness, dryness of the skin, mouth, or other mucus membranes, swelling of the face, hands or feet, muscle inflammation, hair loss, or depression. Women might have irregular or no menstrual periods or a milky nipple discharge. The drug can affect the way the patient’s body makes and keeps new blood cells, so while a patient takes the drug, there is higher chance of getting a serious infection. Thalidomide might cause wounds like cuts or bruises to not heal as fast as they normally would. In addition to these side effects, there is always the possibility of other unknown or severe, side effects, appearing.

Thalidomide may interact with certain drugs such as anti-seizure medications, barbiturates, and alcohol. I must not take barbiturates or drink alcohol while taking thalidomide.

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**Important Information and Warnings for All Patients Taking THALOMID™ (Thalidomide)**

**WARNING: SERIOUS HUMAN BIRTH DEFECTS**
**IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS.**

**CONSENT FOR WOMEN:**

INIT: ___1. I understand I must not take THALOMID™ (thalidomide) if I am pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.

INIT: ___2. I understand that severe birth defects can occur with the use of THALOMID™ (thalidomide). I have been warned by my doctor that my unborn baby will almost certainly have serious birth defects or may even die if I am pregnant or become pregnant while taking THALOMID™ (thalidomide).

INIT: ___3. I understand that if I am able to become pregnant, I must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME:

- **At least one highly effective method**
  - IUD
  - Hormonal (birth control pills, injections, or implants)
  - Tubal ligation
  - Partner’s vasectomy

- **AND**
  - One additional Method
  - Diaphragm
  - Cervical cap

These birth control methods must be used for at least 4 weeks before starting THALOMID™ (thalidomide) therapy, all during THALOMID™ (thalidomide) therapy, and for at least 4 weeks after THALOMID™ (thalidomide) therapy has stopped. I must use these methods even if I am infertile, unless I have had a hysterectomy or because I have been post-menopausal for at least 24 months (been through the change of life). The only exception is if I completely avoid heterosexual intercourse. If a hormonal (birth control pills, injections, or implants) or IUD method is not medically possible for me, I may use another highly effective method or two barrier methods AT THE SAME TIME.

INIT: ___4. I know that I must have a pregnancy test done by my doctor within the 24 hours prior to starting THALOMID™ (thalidomide) therapy, then every week during the first 4 weeks of THALOMID™ (thalidomide) therapy. I will then have a pregnancy test every 4 weeks if I have regular menstrual cycles, or every 2 weeks if my cycles are irregular while I am taking THALOMID™ (thalidomide).

INIT ___5. I know that I must immediately stop taking THALOMID™ (thalidomide) and inform my doctor if I become pregnant while taking the drug; if I miss my menstrual period, or experience unusual bleeding; stop using birth control; or think, FOR ANY REASON, that I may be pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.
INIT__6. I am not now pregnant, nor will I try to become pregnant for at least 4 weeks after I have completely finished taking THALOMID™ (thalidomide).

INIT__7. I understand that THALOMID™ (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are able to have children.

INIT__8. I understand THALOMID™ (thalidomide) can cause side effects including nerve damage (numbness, tingling or pain in the hands or feet that may not be reversible) and drowsiness. (If I become drowsy, I will not operate heavy machinery or drive a car. Also, I will avoid alcohol and other medicines not prescribed by my doctor). If I develop a red itchy rash I will contact my doctor immediately. If I feel dizzy, I will sit upright for a few minutes before standing up from a lying or sitting position. I understand all of the other possible side effects explained to me by my doctor. I know that I cannot donate blood while taking THALOMID™ (thalidomide).

INIT__9. My doctor has answered any questions I have asked.

CONSENT FOR MEN:

INIT__1. I understand that I must not take THALOMID™ (thalidomide) if I cannot avoid unprotected sex with a woman, even if I have had a successful vasectomy.

INIT__2. I understand that severe birth defects or death to an unborn baby have occurred when women took thalidomide during pregnancy.

INIT__3. I have been told by my doctor that I must NEVER have unprotected sex with a woman because it is not known if the drug is present in semen or sperm. My doctor has explained that I must either completely avoid heterosexual sexual intercourse or I must use a latex condom EVERY TIME I have sexual intercourse with a female partner while I am taking THALOMID™ (thalidomide) - and for 4 weeks after I stop taking the drug, even if I have had a successful vasectomy.

INIT__4. I also know that I must inform my doctor if I have had unprotected sex with a woman; or if I think, FOR ANY REASON, that my sexual partner is pregnant. If my doctor is not available, I can call 1-888-668-2528 for information on emergency contraception.

INIT__5. I understand that THALOMID™ (thalidomide) will be prescribed ONLY for me. I must NOT share it with ANYONE, even someone who has symptoms similar to mine. It must be kept out of the reach of children and should never be given to women who are unable to have children.

INIT__6. I understand THALOMID™ (thalidomide) can cause side effects including nerve damage (numbness, tingling or pain in the hands or feet that may not be reversible) and drowsiness. (If I become drowsy, I will not operate heavy machinery or drive a car. Also, I will avoid alcohol and other medicines not prescribed by my doctor). If I develop a red itchy rash I will contact my doctor immediately. If I feel dizzy, I will sit upright for a few minutes before standing up from a lying or sitting position. I understand all of the other possible side effects explained to me by my doctor. I know that I cannot donate blood while taking THALOMID™ (thalidomide).

INIT__7. My doctor has answered any questions I have asked.

Authorization:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor’s instructions, I will not be able to receive THALOMID™ (thalidomide). I now authorize my doctor to begin my treatment with THALOMID™ (thalidomide).

Patient Name (please print) Patient, Parent/Guardian Signature Date (mo./day/yr.)

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ (thalidomide) and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed.
My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

CONTACT PERSONS

If injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. ______________________ the investigator at ______________________ for information regarding patients' rights in research studies.

BENEFITS

The study treatment may keep the brain tumor from growing or may even shrink it. This may provide relief from symptoms and improve my quality of life however this is not guaranteed.

ALTERNATIVES

Alternatives include radiation therapy performed off-study either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy. This would probably result in continued growth of my tumor. My doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my outlook with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, my participation has been voluntary.

CONFIDENTIALITY

Records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, will be sent to a central office for review and research investigation associated with this protocol.
I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or Legal Representative) ___________________  Date ______________

TISSUE AND BLOOD TESTING

I agree to the use of my blood and tumor tissue for additional research studies.

Y Yes       Y No

Patient Signature (or Legal Representative) ___________________  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>

### 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>
<tr>
<td>ORGAN TISSUE</td>
<td>0</td>
</tr>
<tr>
<td>--------------</td>
<td>---</td>
</tr>
<tr>
<td>SKIN</td>
<td>None</td>
</tr>
<tr>
<td>SUBCUTANEOUS</td>
<td>None</td>
</tr>
<tr>
<td>TISSUE</td>
<td>None</td>
</tr>
<tr>
<td>MUCOUS</td>
<td>None</td>
</tr>
<tr>
<td>MEMBRANE</td>
<td>None</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
</tr>
<tr>
<td>SMALL/LARGE</td>
<td>None</td>
</tr>
<tr>
<td>INTESTINE</td>
<td>None</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
</tr>
</tbody>
</table>
APPENDIX IV

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supercede the General Guidelines.

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS
An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

*Known* toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

*Unknown* toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

**Commercial and Non-Investigational Agents**

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. *Known* grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (> grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (> grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

**Investigational Agents**

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)

P. O. Box 30012
Bethesda, MD  20824
Telephone number available 24 hours
*(301) 230-2330      FAX # 301-230-0159*

i.  *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.  Report **by phone** within 24 hours to IDB and RTOG Headquarters.
  **A written report to follow within 10 working days.**

- All deaths within 30 days of termination of the agent.  As above

- All life threatening (grade 4) events which may be due to agent.  As above
- First occurrence of any toxicity (regardless of grade).
  Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.
  **A written report may be required.

ii.  **Phase II, III Studies Utilizing Investigational Agents**

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent.
  Report by phone to RTOG Headquarters and the Study Chairman within 24 hours.
  **A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)**

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.
  Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.
  **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.
  **Report in writing to RTOG Headquarters and IDB within 10 working days.**

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
DCT ADVERSE REACTION FORM FOR INVESTIGATIONAL AGENTS

Person Completing this Form ___________________________ Date ___________________________
Phone (________)  
Physician Responsible for this Report ___________________________ (Please print or type)

I. DEMOGRAPHICS
A. Patient Information
PT I.D.# ____________ Age _____ Sex _____ Date of Initial Dx ___________________________
Malignancy ___________________________ PS (at start of study) ___________________________
Site(s) of Metastatic Disease

Concurrent Non-Malignant Disease and Non-Protocol Medications

B. Drug Information
Drug Name ___________________________
Source of Drug:  NCI _____ Other (specify) ___________________________ Toxicity Grade ______
Type of Reaction ___________________________ Date of Reaction ___________________________
Date IRB Notified ___________________________
NCI Protocol # ___________________________ Attending Physician (Investigator) ___________________________
Phase of Study ___________________________ Institution ___________________________ Phone (____)
Protocol Treatment (include all agents)
Drug ___________________________ Dose ___________________________ Schedule ___________________________ Route

Date First Course Started ___________________________ Number of Courses ___________________________
Date Last Course Started ___________________________ Date of Therapy Associated with ADR ___________________________
Prior Therapy (Drug, radiation, relevant surgery: Include dates of therapy)

II. DOCUMENTATION OF REACTION

A. Non-Myelosuppressive Toxicity and Previously Unknown Myelosuppression
1. Description of Reaction and Temporal Relationship to Investigational Drug Administration

2. Physical Findings and Laboratory Data (e.g., bilirubin, creatinine, including baseline, worst and recovery value) Documenting Toxicity

3. Treatment of Adverse Reaction

4. Past History of Organ Dysfunction

5. Rechallenge with Agent _____ No _____ Yes
If yes: _____ with reaction; describe ___________________________
without reaction

6. Patient outcome: _____ Recovered without sequelae
   _____ Recovered with sequelae; describe _____________________________
   _____ Remains under treatment
   _____ Died; From _____ ADR _____ Malignancy _____ Other ______________________

   Autopsy date _____________________________

B. Myelosuppression (Previously known or unknown)
   1. Laboratory Data Documenting Myelosuppression

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Nadir</th>
<th>Recovery or Latest Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Date/Value</td>
</tr>
<tr>
<td>Date/Value</td>
<td></td>
<td>Date/Value</td>
</tr>
<tr>
<td>Date/Value</td>
<td></td>
<td>Date/Value</td>
</tr>
</tbody>
</table>

   WBC or PMN / / /
   Platelets / /
   Hgb or Hct / /

2. Complications, Treatment and Sequelae (e.g., infections/hemorrhage)

C. Grade of Toxicity and Reporting Requirements (Check one)
   1. Previously Unknown Toxicities:
      a. Fatal _____ or Life-threatening _____ (Report by telephone within 24 hours: 301-230-2330) Date ______
         NCI contact ______
      b. Grade I _____ II _____ III _____ (Send form within 10 days)
   2. Previously Known Non-Myelosuppressive Toxicities:
      a. Fatal _____ or Life-threatening _____ (Send form within 10 days)
   3. Previously Known Myelosuppressive Toxicities:
      a. Fatal _____ (Send form within 10 days)

   Send Forms to: Investigational Drug Branch, NCI
   Post Office Box 30012
   Bethesda, Maryland 20824
   FAX # 301-230-0159

D. Investigator’s Assessment (If more than 1 investigational agent was used, give an assessment for each by writing the drug names on the appropriate lines.)

<table>
<thead>
<tr>
<th>IND Drug</th>
<th>Non-IND Drug</th>
<th>Disease</th>
<th>Action Taken:</th>
<th>Therapy Required:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>_____</td>
<td>_____</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Unlikely</td>
<td>_____</td>
<td>_____</td>
<td>Dose Reduced</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Possible</td>
<td>_____</td>
<td>_____</td>
<td>Dose Withheld</td>
<td>Supportive</td>
</tr>
<tr>
<td>Probable</td>
<td>_____</td>
<td>_____</td>
<td>Drug Discontinued</td>
<td>Intensive</td>
</tr>
<tr>
<td>Definite</td>
<td>_____</td>
<td>_____</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

E. I hereby certify that the information on this form is correct and complete to the best of my knowledge.

__________________________________________ M.D. ______________
(Signature of Responsible Physician) (Date)