

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG BR-0118

### A PHASE III STUDY OF CONVENTIONAL RADIATION THERAPY PLUS THALIDOMIDE (NSC# 66847) VERSUS CONVENTIONAL RADIATION THERAPY FOR MULTIPLE BRAIN METASTASES

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## RADIATION THERAPY ONCOLOGY GROUP

### RTOG BR-0118

#### A PHASE III STUDY OF CONVENTIONAL RADIATION THERAPY PLUS THALIDOMIDE (NSC# 66847) VERSUS CONVENTIONAL RADIATION THERAPY FOR MULTIPLE BRAIN METASTASES

#### SCHEMA

S	<b>*RPA Class</b>	R	<b><u>Arm 1</u></b>
T	1. Class I: < 65 years; no extra-cranial metastases; controlled primary malignancy†	A	Whole Brain Irradiation <sup>a</sup> to 2.5 Gy given daily five days per week ( <i>15 fractions</i> ) for three weeks for a total of 37.5 Gy
R	2. Class II: All other patients	N	
A	<b><u>Chemotherapy Planned</u></b>	D	<b><u>Arm 2</u></b>
T	<b><u>After Whole Brain Irradiation</u></b>	O	Whole Brain Irradiation <sup>a</sup> to 2.5 Gy daily five days per week for three weeks ( <i>15 fractions</i> ) for a total of 37.5 Gy with concurrent thalidomide <sup>b</sup>
I	1. No	M	
	2. Yes	I	
F		Z	
Y		E	

- Cranial irradiation should be delivered using either a clinical set-up to administer whole brain radiotherapy or using an immobilization device and customized shielding to treat a "helmet field." No conedown volumes or stereotactic boost volumes are to be treated.
- (6/10/02)** Thalidomide will be started concurrently with radiation, at a dose of 200 mg p.o. daily at bedtime for one week, and if tolerated, at a dose of 400 mg p.o. daily at bedtime for the second week of cranial irradiation. The dose of thalidomide at bedtime will be increased to 600 mg p.o. for the third week of radiation therapy. After completion of cranial irradiation, the dose will be escalated every two weeks by 200 mg daily to a maximum dose of 1200 mg p.o. daily. Continue for a maximum of two years as long as there is no tumor progression or unacceptable toxicity.

\*See Section 13.5.2

† Controlled primary malignancy defined clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy

#### **Eligibility** (See Section 3.0 for details)

- Histopathologically-confirmed extracranial primary malignancy
- Multiple (>3) brain metastases or a lesser number of metastases with at least one metastasis > 4.0 cm in diameter or metastases to the midbrain or brainstem (*radiosurgery ineligible*) demonstrated on a contrast-enhanced MRI scan of the brain
- No chemotherapy within 2 weeks prior to study entry
- No prior radiation therapy to head and neck area or previous radiosurgery
- No prior treatment with thalidomide
- Estimated survival of at least 8 weeks
- Zubrod 0-1
- Absolute neutrophil count  $\geq 1500$ , Hgb  $\geq 11$ , platelets  $\geq 100,000$ , BUN  $\leq 25$ , Creatinine  $\leq 1.5$ , Bilirubin  $\leq 1.5$ , ALT  $\leq 2$  x normal range
- No history of deep venous thrombosis; no current anticoagulant therapy
- If present, sensory neuropathy must be  $\leq$  grade 1
- No medical illnesses or psychiatric impairments which would prevent completion of protocol therapy
- No pediatric cases
- Not pregnant, not breast feeding, and willing to comply with contraception guidelines
- Patients must sign study-specific consent form prior to study entry.

**Required Sample Size: 332**

RTOG Institution # \_\_\_\_\_

**ELIGIBILITY CHECK** (2/28/02)

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Case # \_\_\_\_\_

\_\_\_\_\_ (Y)1. Does the patient have histopathologically confirmed extracranial primary malignancy?

\_\_\_\_\_ (Y)2. Does the patient have multiple (> 3) brain metastases or a lesser number of metastases with at least one metastasis > 4.0 cm in diameter or metastases to the midbrain or brainstem (*radiosurgery ineligible*) demonstrated on contrast-enhanced MRI of the brain?

\_\_\_\_\_ (N)3. Did the patient have chemotherapy within 2 weeks prior to study entry?

\_\_\_\_\_ (N)4. Did the patient have prior radiation therapy to the head and neck area or previous radiosurgery?

\_\_\_\_\_ (N)5. Has the patient been treated with thalidomide in the past?

\_\_\_\_\_ (Y)6. Does the patient have an estimated survival of at least 8 weeks?

\_\_\_\_\_ (Y)7. Is the Zubrod Performance Scale 0-1?

\_\_\_\_\_ (Y)8. Are pretreatment labs within the parameters specified in Section 3.1.5 of the protocol?

\_\_\_\_\_ (N)9. Does the patient have a history of deep venous thrombosis?

\_\_\_\_\_ (N)10. Is the patient on oral anticoagulant therapy?

\_\_\_ (Y/NA)11. If present, is sensory neuropathy  $\leq$  grade 1?

\_\_\_ (Y/NA) 12. If the patient is female and has childbearing potential, was a negative pregnancy test obtained within 24 hours of start of Thalidomide?

\_\_\_\_\_ (Y) 13. Is the patient  $\geq$  18 years of age?

\_\_\_\_\_ (N)14. Does the patient have known Acquired Immune Deficiency Syndrome?

\_\_\_\_\_ (N)15. Does the patient have major medical illness or psychiatric impairments, which in the investigator's opinion, will prevent administration or completion of protocol therapy?

\_\_\_\_\_ (Y)16. Will this patient be able to be followed regularly by the investigator?

\_\_\_\_\_ (Y)17. Has the patient signed a study-specific informed consent form?

(continued on next page)

RTOG Institution # \_\_\_\_\_

**ELIGIBILITY CHECK (2/28/02)**

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Case # \_\_\_\_\_

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_ (Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- \_\_\_\_\_ 5. Patient's Initials (*Last, First*)
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Ethnic Category
- \_\_\_\_\_ 10. Race
- \_\_\_\_\_ 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*)
- \_\_\_\_\_ (N/Y) 19. Chemotherapy planned after whole brain irradiation?
- \_\_\_\_\_ 20. Treatment Assignment

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

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background**

Despite important advances in diagnosis and therapy of malignant solid tumors, brain metastases continue to present significant problems for clinicians attempting to prevent progression of disease and limit morbidity associated with therapy. There is evidence that the overall incidence of brain metastases is increasing because of improved systemic therapy for cancer.<sup>1</sup> Up to two thirds of all brain metastases are symptomatic at some time during life.<sup>2</sup> Whole brain radiotherapy (WBRT) to treat brain metastases was initiated in 1954.<sup>3</sup> The standard therapy used until this decade has included resection, of solitary metastases, if possible, followed by adjuvant whole brain radiotherapy. Current approaches may include staged craniotomies or stereotactic radiosurgical treatment in addition to WBRT in patients with a limited number of metastases.<sup>4,5</sup> Poor entry of chemotherapeutic drugs into the central nervous system has limited the utility of this therapeutic approach for many patients, and frequently brain metastases develop after the most active systemic therapy has already been given. For patients with lesions too numerous (*or too large*) to reasonably consider stereotactic radiosurgery as a management strategy, options are limited. The focus of this study is the ability of thalidomide to improve survival in patients with multiple or large brain metastases, with secondary endpoints including time to progression, time to neurocognitive progression, cause of death distribution, and frequency of toxicities.

### **1.2 Prior Studies**

Patients treated with WBRT for brain metastases have an extremely poor average survival. This survival is generally anticipated to be between three and six months, and is dependent on a number of factors, such as the extent of systemic disease, general performance status, and the intrinsic radiosensitivity of the tumor.<sup>6-8</sup> For patients with widely disseminated and progressive systemic cancer, the goal of radiotherapy is solely to palliate symptoms for the short remaining lifespan. Survival is not governed in these patients by the failure of radiation to treat the brain lesions, but by the progression of systemic disease. Survival is a crude measure of the effectiveness of WBRT because of the likelihood of dying of systemic cancer progression in a significant number of patients receiving WBRT. Dose fractionation studies carried out by the RTOG have shown that 30 Gy delivered in 10 fractions over 2 weeks resulted in a rate and length of palliation equivalent to more protracted and higher dose schedules.<sup>6-8</sup> Attempts to improve the results of WBRT by the use of hyperfractionation, radiation sensitizers, or other agents have been largely unsuccessful, perhaps because of the problems with controlling systemic disease.<sup>9-11</sup> For some patients presenting with a controlled primary tumor, the issue of uncontrolled CNS metastases is a major factor in determining survival. There are controversies about the number of metastases appropriate for treating with stereotactic radiosurgery (SRS), with most retrospective studies showing that patients with more than three simultaneous metastases are not appropriate for SRS. An recursive partitioning analysis performed on the RTOG database identified two groups of patients with a better prognosis.<sup>20</sup> The patients with the best prognosis are below the age of 65, have a controlled primary malignancy, a normal or near normal performance status, and no extra-CNS metastases. This cohort (RPA class I) has a median survival of 7.1 months. The next best prognosis is seen in the subset of patients who may or may not have controlled systemic disease, but enjoy a normal or near normal performance status. This cohort (RPA class II) has a median survival of 4.2 months. This study hopes to address the use of thalidomide in these two cohorts of patients.

### **1.3 Role of Chemotherapy and Treatment Response Modifiers for Brain Metastases**

Brain metastases often develop in patients who have failed chemotherapy, and most solid tumors metastasizing to the brain have limited responses to currently available systemic therapies. Of the primary tumors that commonly metastasize to the brain, only breast, small cell lung, and germ cell tumors are considered relatively chemosensitive. The presence of the blood-brain barrier can also limit drug access to the central nervous system. Chemotherapy for patients who have brain metastases is commonly the best available systemic therapy for the primary malignancy; intra-arterial therapies are associated with excess toxicity.<sup>12</sup> Patients enrolling as protocol subjects will be stratified by physician intent regarding systemic chemotherapy after cranial irradiation to decrease the chance that more patients in arm 1 are given chemotherapy because of the absence of any other systemic therapy, such as the thalidomide, that patients in arm 2 will receive.

### **1.4 Angiogenesis and Thalidomide**

Angiogenesis or vascular proliferation is required for tumor growth beyond microscopic size. A dozen or more angiogenic factors that act through paracrine and autocrine pathways have been identified in primary malignant tumors and their metastases, and anti-angiogenic therapies are thought to be promising methods to control tumors because of the relative rarity of angiogenesis and neovascularization under normal

conditions.<sup>13-16</sup> Thalidomide is one drug that has been shown to be an extremely effective inhibitor of angiogenesis *in vitro* and in animal systems.<sup>17</sup>

Thalidomide was developed in the 1950's as a sedative that in rodent models was so nontoxic that a LD<sub>50</sub> could not be established. Unfortunately, thalidomide turned out to be a potent teratogen in humans, causing phocomelia and 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 colleagues that thalidomide has potent anti-angiogenic properties.<sup>17</sup>

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 has been performed in patients with recurrent high-grade astrocytomas.<sup>18</sup> 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 the 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 two and nine months, and another 12 patients had stabilization of disease for at least two months. Thus, it appears that thalidomide does have some biologic activity against solid tumors and does have access to the CNS.

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 using thalidomide's ability to inhibit angiogenesis may well be prior to tumor regrowth after radiation therapy. Using this strategy, thalidomide will function as a maintenance agent to prevent tumor regrowth and progression that results from recrudescing tumor-induced angiogenesis.

## **1.5 Quality of Life**

There are scant studies of quality of life in patients with brain metastases. Studies that have reported quality of life generally report on Karnofsky performance status at or above 70%.<sup>19-21</sup> Gambardella et al. used a neurologic classification scale to evaluate the quality of life of brain metastases survivors.<sup>22</sup> The Southwest Oncology Group has used the Spitzer Quality of Life Index (*SQLI*) to measure quality of life in a clinical trial of patients with brain metastases.<sup>23</sup> The current study will utilize the Spitzer Quality of Life Index to measure quality of life (*See Appendix V*).

The *SQLI* is a five-item categorical questionnaire summed in a Likert format with total scores ranging from 0-10. There are no subscale scores for the *SQLI*. The reliability and validity have been established.<sup>24</sup> The *SQLI* has been applied as both a rater-assessed form and a patient self-assessment form. We will be using the *SQLI* as a patient self-assessment form.

RTOG 98-06 evaluated thalidomide concurrent with radiation therapy and in follow up in patients with malignant glioma. Approximately 50% of the patients experienced a grade 3-4 non-hematologic toxicity. The expected rate of grade 3-4 toxicity on the standard arm is less than 5%.<sup>25</sup> The primary endpoint of the current study is improved survival which may come with increased toxicity. Quality of life will be evaluated to determine if improved survival is accompanied with improved quality of life.

## **2.0 OBJECTIVES**

- 2.1** To compare overall survival of patients treated with orally administered thalidomide starting concomitantly with conventional RT to conventional RT alone;
- 2.2** To compare the time to tumor progression between treatment arms;
- 2.3** To compare the time to neuro-cognitive progression between treatment arms;
- 2.4** To compare the cause of death distribution between treatment arms;
- 2.5** To compare the frequency of toxicities between treatment arms;
- 2.6** To evaluate and compare quality of life for patients receiving therapy on the two protocol arms.

### **3.0 PATIENT SELECTION**

#### **3.1 Eligibility Criteria**

- 3.1.1** Histopathologically-confirmed extracranial primary malignancy; Surgical resection of a brain metastasis will not preclude protocol eligibility. The extent of surgical resection in patients having resection of one of multiple metastases 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 post-operative imaging. Radiographically measurable metastatic disease to the brain must be present on a postoperative MRI scan for eligibility for this protocol;
- 3.1.2** Multiple (>3) brain metastases or a lesser number of metastases with at least one metastasis > 4.0 cm in diameter or metastases to the midbrain or brainstem (*radiosurgery ineligible*) demonstrated on a contrast-enhanced MRI scan of the brain;
- 3.1.3** Patients must have an estimated survival of at least 8 weeks;
- 3.1.4** Zubrod of 0-1 (*See Appendix II*);
- 3.1.5** Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 11 grams and the hematocrit is less than 35%, then correction by transfusion and/or erythropoietin is indicated before entry into the study;

*Hematologic:* Hemoglobin  $\geq$  11 grams  
Absolute neutrophil count (ANC)  $\geq$  1500 per mm<sup>3</sup>  
Platelets  $\geq$  100,000 per mm<sup>3</sup>

*Renal:* BUN  $\leq$  25 mg  
Creatinine  $\leq$  1.5 mg

*Hepatic:* Bilirubin  $\leq$  1.5 mg/dL  
ALT  $\leq$  2 x normal range

- 3.1.6** Since thalidomide is a potent teratogen, patients must not be pregnant or nursing, and all patients (*both men and women*) must be willing to practice birth control during, and for at least 4 weeks 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*);
- 3.1.7** The patient must give written study-specific informed consent.

#### **3.2 Conditions for Patient Ineligibility**

- 3.2.1** Grade  $\geq$  2 sensory neuropathy based upon the NCI Common Toxicity Criteria, version 2.0;
- 3.2.2** Major medical illnesses or psychiatric impairments which, in the investigator's opinion, will prevent administration or completion of the protocol therapy;
- 3.2.3** Chemotherapy within 2 weeks prior to study entry;
- 3.2.4** Previous radiotherapy to the head or neck or previous radiosurgery;
- 3.2.5** Patients who cannot be regularly followed by the investigator;
- 3.2.6** Patients with known Acquired Immune Deficiency Syndrome, due to the reported neurologic side effects (*encephalopathy*) in treatment with thalidomide;
- 3.2.7** Patients who have received prior treatment with thalidomide;
- 3.2.8** Patients with a history of deep venous thrombosis or who are on anticoagulant therapy;
- 3.2.9** Patients < 18 years of age, on the basis of safety considerations.

### **4.0 PRETREATMENT EVALUATION**

#### **4.1 Required Evaluations (within 14 days prior to registration) [10/17/02]**

- 4.1.1** Complete history and general physical examination.
- 4.1.2** Detailed neurological examination immediately prior to beginning protocol treatment, including Mini Mental Status Examination and Spitzer Quality of Life Index
- 4.1.3** Steroid and anti-convulsant doses must be documented
- 4.1.4** CBC with differential, platelet count, blood chemistries (*Total protein, albumin, calcium, phosphorus, glucose, BUN, total bilirubin, alkaline phosphatase, ALT, creatinine, uric acid, and LDH*)
- 4.1.5** MRI with contrast (*mandatory for eligibility to document measurable disease*) within 21 days prior to registration

- 4.1.6 Pregnancy test (*in patients in whom conception is possible*); A serum pregnancy test must be done within 24 hours before starting thalidomide.

## **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 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 PARAMETERS**

### **6.1 Dose Definition and Schedule**

Protocol radiotherapy must begin within seven days following registration; if day seven falls on a holiday or weekend, it is acceptable to begin treatment the next business day. One treatment of 2.5 Gy will be given daily 5 days per week (*15 fractions*) for a total of 37.5 Gy over three weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose which shall be the dose on the central ray at mid-separation for two opposed coaxial equally weighted beams.

### **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. 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. **Partial brain conedown, stereotactic, 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 shall include the entire cranial contents, with flashing beyond skin and a minimum margin of 0.75 cm on the skull base as visualized on the simulator or portal films to account for beam penumbra and day-to-day set-up variation. 'Helmet' portals with customized immobilization and shielding are permitted.

### **6.4 Treatment Planning**

Inability to achieve field placement as defined by the protocol will result in variation scores at Headquarters reviews.

### **6.5 Dose Limitation to Critical Structures**

The lens must be shielded from the direct beam at all times, either through primary collimation or through the use of customized shielding. Diode determination of lens doses is acceptable if deemed appropriate by the treating physician.

### **6.6 Documentation Requirements (10/31/03)**

A copy of the pretreatment MRI, treatment calculation form, simulation films (*if done*) and representative portal films of each field must be forwarded to RTOG Headquarters at the completion of treatment. The following shall also be forwarded to Headquarters at completion of treatment: daily treatment record and radiotherapy summary.

### **6.7 Radiation Toxicities (10/31/03)**

- 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 Radiation Toxicity Reporting RTOG AE TELEPHONE LINE: (215) 717-2762 (10/31/03)**

- 6.7.2.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0. A copy of the CTCAE can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). (This protocol will use the CTC 2.0 for AE reporting through December 18, 2003. From December 19, 2003 forward, this protocol will utilize CTCAE 3.0 for AE reporting.)

#### **6.7.2.2 Life-Threatening and Grade 4 Events**

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

#### **6.7.2.3** Fatal Events (Grade 5)

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

**All deaths** during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported by telephone **within 24 hours of discovery** to the RTOG Headquarters AE telephone line, (215) 717-2762 or 1-800-227-5463, X4189. If the event is more than 30 days from completion of radiation treatment, but is felt to be definitely, possibly, or probably resulting from protocol radiation therapy, this event should be telephoned to RTOG Headquarters using the same numbers as listed above.

#### **6.7.2.4** Documentation

Radiation therapy is being combined with thalidomide administration in this protocol, therefore ALL serious adverse events are reported using the appropriate reporting form (AdeERS) as stated in Section 7.8.3 of this protocol.

#### **6.7.2.5** Summary

- Report Grade 4/Grade 5 AE's;
- Telephone report within 24 hours of discovery;
- Document using the appropriate report, AdeERS, within 10 days (a dictated summary and CRF's may also be indicated);
- Institutional reporting as required.

#### DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT

- Telephone report to RTOG within 24 hours of discovery;
- Follow guidelines outlined in Section 7.8.4 of this protocol for AE reporting.

### **6.8** Radiotherapy to Other Sites

**6.8.1** Other (extracranial) sites may receive external beam irradiation as appropriate for the underlying malignancy.

## **7.0** DRUG THERAPY (ARM 2)

### **7.1** Treatment Plan (6/10/02)

Beginning on the same day as radiation therapy for patients randomized to this arm, patients will take four (4) 50 mg hard gelatin capsules (200 mg total dose) of thalidomide at bedtime every night for one week, and if tolerated, a dose of eight (8) 50 mg hard gelatin capsules (400 mg total dose) of thalidomide at bedtime every night for the second week of cranial irradiation. The dose of thalidomide at bedtime will be increased to twelve (12) 50 mg hard gelatin capsules (600 mg total dose) for the third week of radiation therapy. After completion of cranial irradiation, the dose of thalidomide will be escalated every two weeks by 200 mg daily to a maximum dose of 1200 mg per day (24 capsules). Eight weeks of treatment will be considered as one course. This schedule will continue without interruption for a maximum of two years as long as there is no tumor progression and toxicity is acceptable.

For stratification purposes, the intent of the treating medical oncologist must be determined as regards systemic chemotherapy to be commenced immediately after cranial irradiation is completed. For those patients who are to receive systemic chemotherapy as per physician intent, it is recommended that chemotherapy be deferred until 6 weeks after protocol enrollment to allow cranial irradiation to be completed and to allow the patient to recover from the acute sequelae of that irradiation. However, systemic chemotherapy may be commenced within six weeks after protocol enrollment if progression of tumor, either in the CNS, at another metastatic site, or at the primary site, has been documented by clinical or radiological examination and if delaying chemotherapy would be harmful to the patient. Patients who have documented systemic progression, may be started on chemotherapy appropriate to their disease, even

if the original stated intent of the medical oncologist was to not administer chemotherapy after cranial irradiation.

For patients randomized to arm 2 who will be receiving chemotherapy, thalidomide should be given concomitantly with chemotherapy, unless there is toxicity requiring discontinuing of thalidomide, toxicity of combined chemotherapy and thalidomide requiring discontinuation, or if there is intracranial progression.

## **7.2 Drug Information**

### **7.2.1 Thalidomide (NSC# 66847)**

Thalidomide (*N-Phthalidoglutarimide*;  $C_{13}O_4N_2H_9$ ) is a racemate. The S(-)/l and R(+)/d forms represent derivatives of l- and d-glutamic acid, respectively. The maximal solubility of racemic thalidomide in water is approximately  $2 \times 10^4$  mol/L (45 to 60 mg/L). The ultraviolet spectrum of thalidomide is characterized by an absorbance maximum at 300 nm which is dependent on an intact phthalimide moiety. All four amide bonds present in the molecule are susceptible to hydrolytic cleavage *in vitro* at pH values higher than 6 (*Thalidomide Investigator's Brochure*).

Non-enzymatic cleavage of one or more of the amide bonds in the thalidomide molecule produces hydrolysis products which contain at least one carboxyl group. They are thus more polar and can be expected to cross biological membranes less efficiently than the parent compound. Thalidomide constitutes a transport form for its hydrolysis products; the non-polar parent compound enters cells or tissues and is converted to polar derivatives which have been shown to accumulate in erythrocytes and in the embryo. Considering the possible combinations or hydrolysis, hydroxylation and optical activity, there may be more than 50 metabolites of thalidomide *in vivo*.

### **7.2.2 Drug Source and Pharmaceutical Data**

Thalidomide will be provided by CTEP/NCI in 50 mg hard gelatin capsules.

### **7.2.3 Storage**

Thalidomide should be stored at room temperature.

### **7.2.4 Animal Pharmacokinetics**

Studies in experimental animals showed high concentrations of the drug in the gastrointestinal tract, liver, and kidney, and lower concentrations in muscle, brain and adipose tissue. In pregnant animals, thalidomide is able to pass across the placental barrier. In animals, the main pathway of degradation appears to be non enzymatic hydrolytic cleavage. Minor amounts of hydroxylated products have been detected in the urine of some species. Hepatic metabolism of thalidomide probably involves enzymes of the cytochrome P450 family. Only the parent compound is enzymatically modified. Thalidomide itself does not cause enzyme induction, but possibly interferes with enzyme induction caused by other compounds.

### **7.2.5 Human Pharmacology**

Oral administration of thalidomide at 100 to 200 mg in humans results in maximal blood concentrations of 0.9 to 1.5 mg/L after 4 to 6h. Absorption and elimination half-lives calculated from data of eight healthy subjects were  $1.7 \pm 1.05$  and  $8.7 \pm 4.11$  h, respectively; a lag time of  $0.41 \pm 0.17$  h was observed in six individuals. Using a 1-compartment model, the authors calculated a volume of distribution of  $120.64 \pm 45.36$  L, a total body clearance of  $10.41 \pm 2.04$  L/h, and a renal clearance of  $0.08 \pm 0.03$  L/h. Only  $0.6 \pm 0.22\%$  of the administered dose was excreted as unchanged compound in the urine. The hydrolytic cleavage in serum is much slower than *in vitro* at pH 7.4. This may be because thalidomide is highly bound to plasma proteins. Drug interactions with thalidomide have not been systematically studied. Thalidomide enhances the activity of barbiturates, alcohol, chlorpromazine, and reserpine, while its sedative action is antagonized by methyl amphetamine and methylphenidate.

### **7.2.6 Known Toxicities (10/17/02)**

Based on its known immunosuppressive effects, thalidomide has been tested for activity in a number of diseases including acute and chronic graft vs. host disease, leprosy, rheumatoid arthritis, Behcet's disease and recurrent aphthosis in both HIV infected and non-infected individuals. From this extensive experience, the toxicities of the drug are well known (*although not necessarily the mechanism*). The most worrisome of these toxicities is a peripheral neuropathy secondary to axonal dropout. The neuropathy clinically resembles that seen with the vinca alkaloids and is generally not progressive if therapy is terminated in a timely manner. Continued treatment, however, can result in permanent neurologic damage, particularly in patients with a baseline neuropathy. Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide. Other neurologic side effects previously reported are somnolence (referred to as "depressed level of

consciousness” in the NCI Common Toxicity Criteria), confusion, and frank encephalopathy (*the latter having been seen in patients with AIDS*). Other reported side effects have included constipation, dryness of skin and mucosa, swelling of the face and limbs, erythema of the limbs, hair loss, fever, rash, orthostatic hypotension and dizziness, tachycardia or bradycardia, increased appetite, weight gain, loss of libido, nausea, pruritus, and amenorrhea. In addition, cardiopulmonary complications related to blood clots have occurred in some patients taking thalidomide. **NOTE: If a patient suffers a confirmed thromboembolic event (e.g., DVT, PE, TIA, CVA, MI), thalidomide will be immediately discontinued and will not be resumed.**

#### 7.2.7 **WARNING**

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

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

7.2.7.2 Female patients must either abstain from all reproductive sexual intercourse or use two methods of birth control: at least one highly active method (*e.g. intrauterine device [IUD], hormonal [birth control pills, injections, or implants], tubal ligation, or partner’s vasectomy*) and one 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.

7.2.7.3 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 four weeks after discontinuing thalidomide, even if they have had a successful vasectomy.

7.2.7.4 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.”

7.2.7.5 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.”

7.2.7.6 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.”

7.2.7.7 The risk of renal dysfunction may be increased when thalidomide is used in combination with zoledronic acid (Zometa) as indicated in the zoledronic acid package insert. Although described only in myeloma, this precaution could apply to other situations with impaired renal function and/or hypercalcemia. (9/25/03)

### **7.3 Dose Reduction (6/10/02) (2/2/04)**

For peripheral neuropathic toxicity of grade 2 or higher (*see Section 7.2.6*) according to Common Terminology Criteria for Adverse Events Version 3.0, treatment with thalidomide will be immediately stopped. Treatment will be resumed at a 50% dose reduction when the toxicity has resolved to grade 1 or lower. No attempt should be made to increase the dose. Recurrence of dose-limiting peripheral neuropathy on the lower dose or failure to resolve to  $\leq$  grade 1 will permanently discontinue thalidomide.

For dermatological toxicity, thalidomide should be discontinued if a skin rash  $\geq$  grade 2 occurs and only resumed following appropriate clinical evaluation. If the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of thalidomide should not be resumed. Otherwise, therapy may be resumed unless the rash is painful or interfering with patient function. For a grade 3 rash, thalidomide should be held until the toxicity resolves to  $\leq$  grade 1 and then may be restarted at a 50% dose reduction.

For somnolence, thalidomide should be held if a depressed level of consciousness (*NCI Common Toxicity Criteria*)  $\geq$  grade 3 occurs, until the somnolence resolves to  $\leq$  grade 1. Thalidomide then should be restarted at 50% of the prior dose.

For *any* acute toxicity grade 3 or greater (*NCI Common Toxicity Criteria*), thalidomide should be held until the acute toxicity has resolved to grade 1. Thalidomide should then be restarted at 50% of the prior dose. Recurrence of any grade 3 toxicity at the lower dose level or failure of any toxicity to resolve to grade 1 when thalidomide is held should result in permanent discontinuation of thalidomide.

**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 outcome and toxicity. Any patient who progresses clinically during the first eight weeks of therapy will be evaluated by MRI scan and will be considered a protocol failure if CNS disease progression is confirmed by imaging.

**7.6 Accountability and Supply**

**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. 149, Bethesda, MD 20892.

**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 Event Reporting—RTOG AE TELEPHONE LINE (215) 717-2762 or (800) 227-5463 x4189 (10/31/03)**

**7.8.1** This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html> All appropriate treatment areas should have access to a copy of the CTCAE v3.0. See the RTOG procedure manual for general Adverse Event Reporting Guidelines. (This protocol will use the CTC 2.0 for AE reporting through December 18, 2003. From December 19, 2003 forward, this protocol will utilize CTCAE 3.0 for AE reporting.)

**7.8.2** Investigational drug supplied under an NCI-sponsored IND is being used in this study; therefore, all SAEs will be reported using the **Adverse Event Expedited Reporting System** (AdeERS). Reporting requirements and timing of reporting are dependent on the Phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the protocol and/or Investigator's Brochure.

**7.8.3 The following table will outline the reporting requirements for this study**

**Phase II/III Studies**

UNEXPECTED EVENTS		EXPECTED EVENTS	
Grades 2 - 3 Attribution Possible, Probable, or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1 - 3	Grades 4* and 5 Regardless of Attribution
Expedited report within 10 working days.  (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to RTOG Headquarters within 24 hours of discovery.  Expedited report to follow within 10 working days. Death—see 7.X.X	Adverse Event Expedited Reporting NOT required.	Report by phone to RTOG within 24 hours of discovery. Expedited report within 10 working days.  *Grade 4 Myelosuppression events submitted on case report forms.
Note 1	Telephone number available 24 hours daily: (215) 717-2762 or (800) 227-5463, ext. 4189		
Note 2	Report the events using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0		
Note 3	For <b>Hospitalization</b> only – Any medical event equivalent to CTCAE Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.		
Note 4	A list of agent specific expected adverse events can be found in the protocol document and/or consent form.		
Note 5	<b>Reactions considered <i>definitely</i> not treatment-related should not be reported.</b> However, a report should be submitted if there is reasonable suspicion of drug effect.		

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

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

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

**OR**

This Note Can Be Provided If All Deaths On Study Need To Be Reported Via AdEERS: **Note: All deaths on study must be reported using the Adverse Event Expedited Reporting System (AdEERS) regardless of causality. Attribution to treatment or other cause should be provided.**

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

## **7.9 Clinical Trials Agreement**

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**

Not applicable to this study.

## **9.0 OTHER THERAPY (6/10/02)**

Chemotherapy is not recommended within 6 weeks after study entry to allow cranial irradiation to be completed and to allow the patient to recover from the acute sequelae of that irradiation, unless tumor progression is documented and if delaying chemotherapy would be harmful to the patient. Beyond 6 weeks after study entry, systemic chemotherapy is acceptable and is at the treating physician's discretion. Thalidomide should be given concomitantly with chemotherapy, unless there is toxicity requiring discontinuing of thalidomide, toxicity of combined chemotherapy and thalidomide requiring discontinuation, or if there is intracranial progression.

Patients enrolling as protocol subjects will be stratified by physician intent regarding systemic chemotherapy after cranial irradiation to decrease the chance that more patients in arm 1 are given chemotherapy because of the absence of any other systemic therapy, such as the thalidomide, that patients in arm 2 will receive.

Somnolence (*referred to as "depressed level of consciousness" in NCI CTC criteria*) is a common side effect of thalidomide. Caffeine can be used to treat mild somnolence from thalidomide during radiation therapy. After radiation therapy is completed and when a stable dose of thalidomide is reached, either Ritalin (methylphenidate) or Provigil (modafinil) may be of benefit in treating drug-induced somnolence.

A recommendation is made for a prophylactic bowel regimen to treat constipation, which is a common side effect of thalidomide. This should be instituted at the time that thalidomide therapy is started or for mild (*grade 1*) symptoms.

## **10.0 PATHOLOGY**

Not applicable to this study.

## **11.0 PATIENT ASSESSMENTS**

### **11.1 Study Parameters (6/10/02)**

<b>Assessment</b>	<b>Pre-entry</b>	<b>Radiotherapy</b>	<b>Thalidomide Therapy</b>		
			<b>weekly</b>	<b>q 2 wks</b>	<b>q 8 wks</b>
History & Physical	X				X <sup>k</sup>
Neurological Exam and QOL assessment	X <sup>g</sup>	X <sup>i</sup>		X <sup>h</sup>	X <sup>k</sup>
Record Steroid Dose	X	X		X	X
Anticonvulsant Level <sup>f</sup>	X				X
CBC, Diff, Plts	X	X		X <sup>b</sup>	X <sup>j</sup>
Blood Chemistries <sup>d</sup>	X			X <sup>b</sup>	X <sup>j</sup>
MRI with contrast	X				X <sup>c</sup>
Serum bHCG pregnancy test <sup>e</sup>	X		Weekly x first 4 wks, then q 4 wks		
Toxicity Evaluation		X <sup>a</sup>		X	X

- Weekly during XRT
- Every 2 weeks during thalidomide dose escalation or reduction (*See Section 11.2.5*) [6/10/02]
- Initial follow-up MRI scan to be done one month after completion of radiotherapy or at the time of neurologic deterioration, if between routine follow-up MRI scans. **Note: It is mandatory that patients are followed with MRI scans.**

MRI should include the following: pre-contrast sagittal T1, axial T1 without and with contrast, axial T2, and coronal T1 post-contrast. For T1 weighted images, axial slice thickness should be 5 mm/skip 1 mm, with image acquisition parallel to the AC/PC line. Sagittal slice thickness should be 5 mm/skip 1 mm. Coronal slice thickness should be 5 mm/skip 1 mm with image acquisition perpendicular to the AC/PC line. For T2 weighted images, axial slice thickness should be 5 mm/skip 2.5mm.

- Total protein, albumin, calcium, phosphorus, glucose, BUN, total bilirubin, alkaline phosphatase, ALT, creatinine, uric acid, and LDH.
- As applicable for women of child-bearing potential; Also, see Section 11.2.4 for testing schedule during thalidomide therapy.

- f. Researchers should disregard this requirement for patients on gabapentin.
- g. Includes MMSE and SQLI (**PQ or PF**; See Section 12.0)
- h. Does not include MMSE and SQLI
- i. MMSE and SQLI (**PF**) at completion of radiotherapy
- j. Every 8 weeks during stable dose of thalidomide (See Section 11.2.5) [6/10/02]
- k. Follow up includes history/physical, Mini Mental Status Exam (**MS**), and Spitzer Quality of Life (**PF**) every 2 months from treatment start for year 1; then history/physical and Mini Mental Status Exam every 4 months for a year, every 6 months for two years, then annually for the patient's lifetime. (6/10/02)

## **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 maintenance thalidomide therapy (See 11.1 for inclusion of MMSE in neurological examination).
- 11.2.2** Skin within the treatment portal shall be examined at least once a week during radiation therapy.
- 11.2.3** A Gadolinium enhanced MRI of the brain shall be obtained prior to radiotherapy, every two months during thalidomide 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 ten weeks post treatment and last up to six to eight weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination.<sup>26</sup> Caution is therefore urged in diagnosing and treating recurrent tumor during the first two to three months post irradiation.
- 11.2.4** **Within 24 hours prior to the initiation of thalidomide, all female patients of child bearing potential must have a negative serum bHCG pregnancy test. In addition, a pregnancy test should be performed weekly for the first four weeks after the initial dose of thalidomide.** Monthly serum bHCG pregnancy tests are required while receiving thalidomide as long as menstrual periods are normal and every two weeks if menstrual periods are irregular. Female patients of childbearing age should use two simultaneous methods of contraception if participating in heterosexual sexual intercourse. One of these methods must include at least one highly-effective method (e.g. *intrauterine device [IUD], hormonal contraception, tubal ligation, partner's vasectomy*) and one additional effective method (e.g. *latex condom, diaphragm, cervical cap*). A hysterectomy, no menses, or having been postmenopausal for at least 24 months will obviate the necessity for two simultaneous methods of contraception. Pregnancy testing should be done four weeks after the final dose of thalidomide and whenever the patient misses a menstrual period. In addition, because it is not known whether or not thalidomide is in male ejaculate, male patients who have not had a vasectomy must be willing to refrain from reproductive sexual intercourse or use a condom while taking thalidomide and for at least one month after the final dose of thalidomide.
- 11.2.5** While a patient is on a stable dose of thalidomide, CBCs and serum chemistry studies are required every 8 weeks. While a patient is not receiving a stable dose of thalidomide (e.g. dose escalation or dose reduction of thalidomide), CBCs and serum chemistries should be repeated every 2 weeks. (6/10/02)
- 11.2.6** Appropriate radiographic evaluation of the venous circulation shall be performed in patients with signs or symptoms suggestive of deep venous thrombosis. In addition, evaluation of cardiac function and pulmonary artery blood flow will be performed in patients with signs or symptoms of pulmonary emboli. (10/17/02)

## **11.3 MRI Review**

The serial MRI 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):** The tumor is no longer seen on two sequential MRI scans, and the patient is on no steroids or only adrenal-maintenance doses of steroids.
- 11.4.2** **Partial Response (PR):** Decrease of  $\geq 50\%$  in the product of two diameters on two sequential MRI scans, 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  $< 50\%$  on two sequential MRI scans provided that the patient has not had his/her dose of steroids increased since the last evaluation period
- 11.4.4** **Stable Disease (SD):** The scan shows no change. Patients should be receiving stable or decreasing doses of steroids.

**11.4.5** Progression (P): 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.

**11.4.6** Patients with a radiographic CR or a PR must have MRI scans every two months to follow the CNS disease status. The second MRI scan confirming an apparent radiographic CR or PR is vitally important to the definition of radiographic partial or complete response.

### **11.5 Criteria for Evaluation of Therapy Effectiveness**

**11.5.1** Overall survival will be measured from the time of starting radiotherapy until death.

**11.5.2** Tumor response and regrowth frequently can be difficult to measure directly. Neurological exams and MRI 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 consistently be followed with the same diagnostic imaging study (*MRI*).

**11.5.3** The time to neuro-cognitive progression will be documented by evaluation with the MMSE as indicated in Section 11.1.

**11.5.4** Quality of life will be measured using the Spitzer Quality of Life Index (*SQLI*). The SQLI is given to the patient at the same time points as the MMSE during the first year on study.

**11.5.5** Cause of death will be reported for evaluation of cause of death distribution (*e.g. death from CNS progression vs. death from systemic disease progression, etc.*)

## **12.0 DATA COLLECTION**

### **12.1 Summary of Data Submission (10/31/03)**

*(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX # 215/928-0153)*

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form ( <b>A5</b> )	Within two weeks of registration
On-study Form ( <b>I1</b> )	
Pathology Report ( <b>P1</b> )	
Mini Mental Status Exam ( <b>MS</b> )	
Spitzer Quality of Life Index ( <b>PQ</b> )	
<u>Dosimetry Information:</u>	Within one week of completing radiotherapy
Pretreatment MRI ( <b>MR</b> ) and Report ( <b>ME</b> )	
Calculation Form ( <b>TL</b> )	
Daily treatment record ( <b>T5</b> )	
Simulation ( <i>if applicable</i> ) & Port films of all fields ( <b>TP</b> )	
Radiotherapy Form ( <b>T1</b> )	Every 2 months during drug administration
Mini Mental Status Exam ( <b>MS</b> )	
Spitzer Quality of Life Index ( <b>PF</b> )	
Treatment Summary Form ( <b>TF</b> )	Every 2 months during drug administration
Initial Follow-up Form ( <b>FS</b> )	At completion of RT and 90 days after RT
Follow-up Form ( <b>F1</b> )	Every 2 months from treatment start for year 1; q 4 months x 1 year; q 6 months x 2 years, then annually; Also at progression/relapse and at death. The SQLI is collected only during the first year of follow up.
Mini Mental Status Exam ( <b>MS</b> )	
Spitzer Quality of Life Index ( <b>PF</b> )	
Post-treatment MRI ( <b>MR</b> ) and Report ( <b>ME</b> )	One month post-RT; for grade > 3 RT toxicity and for progression.
Operative reports ( <b>S2</b> ), surgical reports ( <b>S5</b> ) ( <i>for subsequent surgery</i> )	As applicable
Autopsy Report ( <b>D3</b> )	As applicable

## **12.2 MRI Documentation**

The contrast-enhanced MRI done before radiotherapy begins must be submitted within two weeks of registration. The initial post-RT scan will be done at one month after the completion of radiotherapy and must also be submitted to Headquarters. A MRI must be done at the time of neurologic deterioration, suggestive of tumor recurrence and not related to lowered steroid dose, unless the last MRI had been done within one month and was compatible with recurrence. **The patient should consistently be followed with MRI.** 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**

### **13.1 Study Endpoints**

- 13.1.1 Overall survival.
- 13.1.2 Time to tumor progression.
- 13.1.3 Time to neuro-cognitive progression.
- 13.1.4 Cause of death distribution.
- 13.1.5 Frequency of toxicities.
- 13.1.6 Quality of life.

### **13.2 Sample Size**

#### **13.2.1 Survival**

The primary endpoint of this study is survival. The standard arm is radiotherapy (RT) alone. The experimental arm is RT and thalidomide. The estimate for the median survival time (MST) for the RT-alone arm is based upon the mix of patients from the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classes.<sup>27</sup> Assuming the mix is 20% RPA Class I and 80% Class II then the baseline MST is estimated to be 4.57 months. The alternative hypothesis is a difference between the two arms of at least 35%. A sample size of 158 eligible patients per arm will provide overall statistical power of 80% with a one-sided significance level of 0.05. Using EaSt statistical software (*version 1.0, Cytel, 2000*), the estimated sample size includes the following parameters: shape parameter of 0.20, 14.5 months of accrual and 6 months of follow up. Since it is expected that 5% of the patients will be ineligible, then **a total of 332 patients will be required.**

According to Gaspar et al. the recursive partitioning analysis classes are prognostically important.<sup>27</sup> Based upon eligibility criteria, patients may be in RPA Classes I or II which have distinct estimated MST from 7.1 to 4.2 months, respectively. The mix of RPA Classes was examined for the influence on sample size. It was determined that a range of 10-40% in the proportion of RPA Class I patients in the sample did not affect the overall sample size.

#### **13.2.2 Tumor Progression**

Time to tumor progression is measured from the date of randomization to documentation of progression as previously defined in the protocol. It is expected that the reduction in hazard rate for progression will be greater than or equal to that in survival. The literature for time to tumor progression is difficult to interpret for this endpoint because of advances in imaging, variations in definitions, and inter-rater variability. Furthermore, the cumulative incidence model<sup>28</sup> will be used to analyze this data, and no current sample size methodology exists for this model.

#### **13.2.3 Neurocognitive Progression**

The MMSE will be used to determine neurocognitive progression. The MMSE is affected by age and years of education. An age- and education-adjusted cutoff level will be used to define patients with possible cognitive dysfunction.<sup>29</sup> Patients with MMSE at or below the cutoff will be considered cognitive failures. The cutoff points have been shown to have a sensitivity of 82% and a specificity of 98% for identifying cognitive dysfunction by MMSE. The cumulative incidence model will be used to analyze the time to neurocognitive progression.

#### **13.2.4 Cause of Death**

The expected number of deaths is 227. It is anticipated that each arm will have at least 100 deaths. The RT-alone arm is expected to have 37% of the death due to brain metastases. There will be 80% statistical power to detect at least a reduction of 17% (*to 20%*) in deaths due to brain metastases for RT+thalidomide, using a one-sided significance level (*0.05*).

#### **13.2.5 Toxicities**

The toxicity profile will be compared between treatment arms. In RTOG 91-04, which had brain metastases patients treated with RT alone, 2% of the patients experienced a grade 3-5 toxicity. This

study will have 90% statistical power to detect an actual 6.7% increase in grade 3-5 toxicity rates for RT+ thalidomide.

**13.2.6 Quality of Life**

Quality of life will be measured by the Spitzer Quality of Life Index (SQLI). Previous RTOG studies have indicated that a 0.5 point difference in SQLI scores was clinically meaningful.<sup>30</sup> A common standard deviation of 0.54 is assumed for SQLI. It is estimated that 80% of the patients alive at six months will have a SQLI assessment at six months. If there is a survival difference, then the sample size will be unequal at six months. However, the above sample size will be sufficient to provide at least 90% statistical power to detect a clinically meaningful difference in SQLI between the two treatment arms at both six and 12 months.

**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 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.<sup>27</sup> 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.

**Planned Gender and Minority Inclusion**

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Total
Female	1	2	18	8	0	137	166
Male	1	2	18	8	0	137	166
Total	2	4	36	16	0	274	332

**13.4 Patient Accrual**

The patient accrual is projected to be 23 cases per month. At that rate, it will take 14.5 months to reach the required total accrual of cases.

**13.5 Randomization**

**13.5.1** Patients will be randomized according to a permuted block design, balancing by institution within strata. The randomization will be stratified by RPA (*Class I vs. Class II*) and planned chemotherapy (*yes vs. no*).

**13.5.2** RPA Class I is defined as patients with KPS  $\geq$  70 (*Zubrod 0-1*); age < 65 years; no extra-cranial malignancies; and controlled primary malignancy (*controlled primary malignancy is defined clinically, radiographically, and/or serologically, as appropriate for the underlying malignancy:*). RPA Class II is defined as all eligible patients which do not fall into RPA Class I; in other words, patients with KPS  $\geq$  70 and any of the following: age  $\geq$  65; extra-cranial metastases; or uncontrolled primary malignancy. **Note:** Since all patients are required to have KPS  $\geq$  70 to enter the study, this factor is not listed in the stratification definitions.

**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;
- b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of the toxicities;
- d) the distribution of patients by pretreatment characteristics including RPA classes.

**13.6.2 Interim Analyses of Endpoints**

There will be one interim analysis of the primary study endpoint (*survival*). The interim analyses will proceed according to the following table.

**Total Accrual**  
50%

**Significance Level**  
0.0077

If a significance level is smaller than the value listed, then the null hypothesis will be rejected. This significance level was calculated to ensure an overall significance level of 0.05. There will be one stochastic analysis<sup>31</sup> at 50% accrual. If the stochastic analysis indicates less than 15% power to observe the alternative hypothesis, then it will be recommended that the study be closed. The results of these interim analyses will only be reported in a blind fashion to the Data Monitoring Committee.

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

This analysis will be undertaken when all patients potentially have been followed for a minimum of six months. An intent-to-treat analysis will be performed excluding only patients that were ineligible for the protocol. 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 institutional accrual;
- c) distribution of important prognostic baseline variables by treatment arm;
- d) observed results with respect to the endpoints described in Section 13.1.

The p-value for tests of endpoints will be 0.0492, adjusting for the interim analysis.

**13.6.4** Survival

RT alone will be compared to RT+thalidomide using the log-rank statistic. Analyses within RPA classes will be performed. Additional subgroup analyses will be performed if there are sufficient numbers of patients. RPA class will be included in a multivariate Cox model along with treatment arm to test the relative importance of these factors for survival.

**13.6.5** Tumor Progression

Survival is made up of two components: time spent without tumor progression and time spent with tumor progression. For this reason, time to tumor progression is correlated with survival. We expect the results to be closely reflective of survival. However, not all patients will have documented tumor progression at death or during survival which may account for differential outcome. Time to tumor progression will be computed using the cumulative incidence model. Analyses within RPA classes will be performed. Analyses within other prognostic groups may be performed if there are sufficient numbers of patients. A multivariate Cox model analysis will also be performed including RPA class, treatment assignment, and other important prognostic factors.

**13.6.6** Neurocognitive Progression

Time to neurocognitive progression will be computed as the time to MMSE score dropping by one point from baseline. This analysis will be performed using the cumulative incidence model. A multivariate Cox model will also be performed including RPA class, treatment assignment, and other important prognostic factors.

**13.6.7** Cause of Death

Cause of death will be determined for all patients. The frequency of brain metastases-related deaths will be computed for each treatment arm. The two arms will be compared using the Pearson chi-square test.

**13.6.8** Toxicity

Overall toxicity will be compared across treatments. The comparison will be performed using the Pearson chi-square test.

**13.6.9** Quality of Life

Quality of life change scores from baseline will be computed. Comparison between the treatment arms at 6 months and 12 months will be performed using a t-test. An area under the curve analysis will be performed at 12 months capturing all SQLI obtained during the first year. The arms will be compared using a z-test.

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## **APPENDIX I**

### **RTOG BR-0118**

#### **SAMPLE CONSENT FOR RESEARCH STUDY**

##### **STUDY TITLE**

#### **A PHASE III STUDY OF CONVENTIONAL RADIATION THERAPY PLUS THALIDOMIDE (NSC# 66847) VERSUS CONVENTIONAL RADIATION THERAPY FOR MULTIPLE BRAIN METASTASES**

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

You are being asked to take part in this study because you have cancer that has spread to the brain.

##### **WHY IS THIS STUDY BEING DONE?**

The usual treatment in cancer that has spread to the brain is radiation therapy. In this study, radiation therapy alone will be compared to radiation therapy combined with the investigational drug thalidomide (during and after radiation therapy). This will help us know whether thalidomide, which has been shown to decrease blood supply to some tumors and slow their growth, helps patients who receive the drug. This research is being done because the standard treatments for cancer that has spread to the brain are not always effective.

This study will also gather information as to whether the addition of the drug thalidomide affects the time to regrowth of the cancer, information about the function of the brain before and after the two treatments, and side effects of therapy. In addition, the study will gather information about the quality of your life.

In some patients with cancer that has spread to the brain, chemotherapy is used in addition to radiation therapy. This is not encouraged for patients two weeks before participating in this study or in the first six weeks of this study, unless there is evidence that radiation therapy (with or without thalidomide) has not been effective and your cancer progresses. You may receive chemotherapy within the first six weeks of this study if progression occurs. You also may receive chemotherapy after you have been participating in the study for at least six weeks, if you and your doctor feel that chemotherapy is appropriate. Such chemotherapy will not be provided as part of this study.

## **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 332 people will take part in this study.

## **WHAT IS INVOLVED IN THE STUDY?**

This study involves assignment to one of two treatments. It is not clear at the present time which of the two treatments is better. For this reason the therapy offered to you will be based upon a method of selection called randomization.

Randomization means that you are put into a group by chance. A computer will assign you to one group. You will have an approximately equal chance of being assigned to one of the following treatments:

### **Treatment 1**

You will receive radiation therapy once a day, five days a week (*Monday to Friday*) for three weeks, for total of fifteen treatments.

### **Treatment 2 (6/10/02)**

You will receive radiation therapy once a day, five days a week (*Monday to Friday*) for three weeks, for total of fifteen treatments. In addition, you will begin taking thalidomide on the first day of radiation treatment and will continue taking thalidomide at the highest, well-tolerated dose (to a maximum of 24 hard gelatin capsules) for up to two years or until your doctor tells you to stop. To start, you will take four thalidomide pills every evening at bedtime (*by mouth*). After the first week of radiation therapy, you will double the dose of thalidomide to eight pills every evening at bedtime (*by mouth*). During the final week of radiation therapy, your dose will increase to twelve pills a night. Your nightly thalidomide dose will increase by four pills every two weeks after that, to a maximum of twenty-four pills a night, provided you experience no serious side effects.

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

- A physical examination before you begin treatment and every two months to evaluate the tumor and the effects of treatment
- A brief questionnaire before treatment, weekly during radiation therapy, every two weeks for six weeks for those individuals receiving thalidomide then every two months; The questionnaire measures your thinking abilities by asking you to answer questions and follow a few directions.
- A brief questionnaire before treatment, at the end of radiation therapy, then every two months for a year; the questionnaire asks about the quality of your life.
- Blood tests before beginning treatment, during treatment, and every two months

- For women of childbearing age assigned to Treatment 2, pregnancy testing every week for the first month of treatment and then at least monthly thereafter
- You will have an MRI before treatment and then every eight weeks, a repeat MRI will be done.
- A neurological exam will be done once a week during radiation therapy, every 2 weeks during thalidomide dose increase or decrease, and every 2 months during maintenance thalidomide therapy.

All of these tests and procedures can be performed on an outpatient basis; no hospitalization is necessary.

The Division of Cancer Treatment, National Cancer Institute will provide thalidomide free of charge for this study.

### **HOW LONG WILL I BE IN THE STUDY? (6/10/02)**

Patients in both treatment groups will receive radiation therapy for three weeks; patients in Treatment 2 will also take thalidomide for up to two years. Follow up will take place every two months from the start of treatment for the first year, then every 4 months for a year, then every 6 months for 2 years, then annually for your lifetime.

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest, if funding for this study is stopped, if the drug supply is insufficient, or your condition worsens. You may also be taken off this study if new information becomes available about how to better treat cancer that has spread to the brain.

### **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 researcher 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 study treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

#### **Whole Brain Radiation Therapy**

##### *Very Likely*

Hair loss, which may be permanent

Dry mouth and/or change in taste

Headaches

Nausea and/or vomiting

Scalp reddening or tanning and irritation (Your skin will be examined once a week during radiation therapy)

Tiredness

Less Likely But Serious

Temporary worsening of tumor symptoms such as seizures or weakness  
Drainage from the ears or plugging of the ears with decreased hearing  
Memory loss, behavioral change and/or increased sleepiness (occurring four to ten weeks after radiation therapy is complete and lasting for several days up to two weeks)  
Cataracts and eye damage with the possibility of blindness  
Severe local damage to normal brain tissue (*necrosis*), which may require surgery

**Risks from Thalidomide (10/17/02)**

Very Likely

Sleepiness and decreased alertness  
Fatigue  
Constipation/hard or infrequent bowel movements (Your doctor will recommend a regular program of stool softeners.)  
Increased appetite; weight gain  
Decreased sex drive  
Nausea (vomiting)  
Redness of skin; skin rash; itchiness  
Dryness of skin, mouth, or linings of other body openings or canals open to the air  
Hair loss  
Numbness, tingling, or pain in hands or feet caused by damage to the nerves that may be permanent  
Thyroid problems  
Heart irregularities  
Bladder infection  
Blood irregularities (such as anemia)  
Respiratory difficulties  
Bone pain

Less Likely

Weight loss  
Decreased ability to sleep  
Muscle weakness  
Mood changes; depression  
Confusion  
Fever  
Swelling of the face, hands, or feet  
Irregular menstrual periods  
Milky nipple discharge  
Decreased healing of cuts or bruises

*Less Likely But Serious*

Low blood pressure and dizziness (Therefore, you should sit upright for a few minutes before standing up from a reclining position to avoid falling.)  
Rapid heartbeat  
Increased risk of infection due to low blood counts  
Blood clots in legs and lungs

*Rare*

Decreased coordination while walking  
Inflammation of the eye  
Slow heart rate  
Changes in blood sugar  
Problems with heart or lung function from blood clots moving from the veins in the body to the lungs  
Low platelets (may make you more likely to have bleeding and bruising)  
Seizures or other brain disorders  
Severe rash called Stevens-Johnson syndrome, which can cause fever and red sores in your mouth and eyes

Thalidomide may worsen sleepiness associated with certain drugs such as some anti-seizure medications, barbiturates (sleeping aids), and alcohol. Your doctor may give you other anti-seizure medications. You must not take barbiturates or drink alcohol while taking thalidomide. You must use caution when driving or operating machinery.

The risk of kidney problems may be increased when zoledronic acid (Zometa) is used in combination with thalidomide. Although this warning, which is indicated on the drug information (a piece of paper) inserted in the package of zoledronic acid, has been described only in patients with myeloma (a type of cancer in the bone and bone marrow), it could apply to other situations when these drugs are used in patients with kidney problems and/or hypercalcemia (too much calcium in the blood). (9/25/03)

Thalidomide causes severe birth defects in unborn babies if pregnant women take it. The risk of thalidomide causing damage to the embryo is up to 50% for women taking thalidomide during the “sensitive period,” which is estimated to range from 35-50 days after the last menstrual period. It is not known whether thalidomide may cause birth defects in unborn babies if it is taken after the “sensitive’ period. A single dose of thalidomide may cause birth defects.

Birth defects observed in babies exposed to thalidomide during pregnancy include absent or abnormal legs and arms; spinal cord defects; cleft lip or palate; absent or abnormal external ear; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system, including blockage of necessary openings. In addition, there has been an association described between thalidomide and autism (a mental disorder characterized by extreme withdrawal and an abnormal absorption in fantasy).

Because of the severity of these abnormalities, it is extremely important that pregnancies do not occur while you are taking thalidomide. Thalidomide has been found in the semen of men taking thalidomide. (10/17/02)

You should discuss with your doctor what the best methods of birth control are for you. Remember, however, that **no** method of birth control besides complete abstinence provides 100% protection from pregnancy.

**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**

Latex condom

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 of 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 able to have children.

INIT \_\_\_6. I understand THALOMID™ (*thalidomide*) can cause side effects including nerve damage (*numbness, tingling or pain in the hands of 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.

\_\_\_\_\_  
Physician Name (*please print*)

\_\_\_\_\_  
Physician Signature Date (*mo./day/yr.*)

A booklet from the manufacturer of thalidomide, "THALOMID™ (*thalidomide*): Balancing the Benefits and the Risks," is available from your doctor.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

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

Treatment with radiation (with or without thalidomide) may keep the brain tumor from growing and may shrink it. This may provide relief from symptoms and

improve your quality of life. Thalidomide may improve control of the brain tumors. However, neither of these benefits is guaranteed.

### **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; or (3) no treatment except medications to make you feel better. With the latter choice, your tumor could continue to grow and your disease could spread. These treatments could be given either alone or in combination with each other.

Comfort Care only: treatments are directed only at reducing symptoms, relieving suffering, and maximizing comfort, dignity, and control. Treatment is not directed at curing, slowing, or reversing your disease. Please ask any questions you may have, and take as much time as you need to make a decision.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

### **WHAT ABOUT CONFIDENTIALITY?**

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

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*) or its authorized representatives, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

### **WHAT ARE THE COSTS?**

The Division of Cancer Treatment and Diagnosis, National Cancer Institute, will provide you with thalidomide free of charge for this study. Every effort has been made to ensure adequate supplies of thalidomide, free of charge, for all participants. If, however, this investigational agent becomes commercially available for cancer that has spread to the brain while you are being treated, there is a possibility that you would be asked to purchase subsequent supplies.

Your doctor may prescribe medication to keep side effects under control, which could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment. Laboratory testing and procedures required by this study for research purposes may increase your medical bills although the impact will be dependent on your insurance company. Taking part in this study may lead to added costs to you or your insurance company. Medicare should be considered a health insurance provider. 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.

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

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may 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

You also may call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-549-0715 (from the continental U.S. only) or 800-937-8281, ext. 4445 (from sites outside of the continental U.S.).

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

### **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  
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ  
<http://cancernet.nci.nih.gov>.

CancerFax: Includes NCI information about cancer treatment, screening, prevention, and supportive care; to obtain a contents list, dial 301-402-5874 or 800-624-2511 from a fax machine hand set and follow the recorded instructions.

### **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 Signature (*or legal Representative*)

\_\_\_\_\_

Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

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

### **ZUBROD PERFORMANCE SCALE**

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

**APPENDIX III (10/31/03)**

**SPITZER QUALITY OF LIFE INDEX**

**A. ACTIVITY**

**DURING THE LAST WEEK I HAVE:**

2

been carrying out my normal activities, working or studying full-time, or nearly so, in usual occupation; or managing own household; or participating in unpaid voluntary activities, whether retired or not

1

been working or studying, in usual occupation or managing own household or participating in unpaid volunteer activities but requiring major assistance or significant reduction in hours worked or a sheltered situation or was on sick leave

0

not been working or studying in any capacity and not managing own household

**B. DAILY LIVING**

**DURING THE LAST WEEK I HAVE:**

2

been self-reliant in eating, washing, toileting and dressing; using public transportation or driving

1

been requiring assistance (another person or special equipment) for daily activities and transportation but performing light tasks

0

not been managing personal care nor light tasks and/or not leaving own home or institution at all

**C. HEALTH**

**DURING THE LAST WEEK I HAVE:**

2

been appearing to feel well or reporting feeling "great" most of the time

1

been lacking energy or not feeling entirely "up to par" more than just occasionally

0

been feeling very ill or "lousy", seeming weak and washed out most of the time

**D. SUPPORT**

**DURING THE LAST WEEK I HAVE:**

2

been having good relationships with others and receiving strong support from at least one family member and/or friend

1

received or perceived the support from my family and friends as being limited which may be related to my condition

0

received support infrequently or only when absolutely necessary

**E. OUTLOOK**

**DURING THE LAST WEEK I HAVE:**

2

usually been appearing calm and positive in outlook, accepting and in control of personal circumstances, including surroundings

1

sometimes been troubled because not fully in control of personal circumstances or has been having periods of obvious anxiety or depression

0

been seriously confused or very frightened or consistently anxious and depressed