A PILOT PHASE II STUDY OF PRE-OPERATIVE RADIATION THERAPY AND THALIDOMIDE (IND 48832; NSC 66847) FOR LOW GRADE PRIMARY SOFT TISSUE SARCOMA OR PRE-OPERATIVE MAID/THALIDOMIDE/RADIATION THERAPY FOR HIGH/INTERMEDIATE GRADE PRIMARY SOFT TISSUE SARCOMA OF THE EXTREMITY OR BODY WALL

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SCHEMA

<table>
<thead>
<tr>
<th>Grade</th>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grade 3-4</td>
<td>High/Intermediate Grade</td>
<td>Low Grade</td>
</tr>
<tr>
<td>2. Grade 1-2</td>
<td>Histology grade 3 or 4 (AJCC, 6th edition)</td>
<td>Histology grade 1 or 2 (AJCC, 6th edition)</td>
</tr>
</tbody>
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TREATMENT

COHORT A

<table>
<thead>
<tr>
<th>MAID</th>
<th>RT/THAL</th>
<th>MAID</th>
<th>RT/THAL</th>
<th>MAID</th>
<th>Surgery</th>
<th>Post-op Adj. THAL for 12 months Post-op Boost RT if positive margin</th>
</tr>
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<tbody>
<tr>
<td>MAID</td>
<td>RT/THAL</td>
<td>MAID</td>
<td>RT/THAL</td>
<td>MAID</td>
<td>Surgery</td>
<td>Post-op Adj. THAL for 12 months Post-op Boost RT if positive margin</td>
</tr>
</tbody>
</table>

Cohort A: Neoadjuvant MAID (Mesna, Doxorubicin, Ifosfamide, DTIC) x 3 cycles with Concurrent thalidomide and radiation therapy (RT) x 2 cycles Followed by surgical resection and Adjuvant thalidomide for 12 months (post-op boost RT if positive margin; see Section 6.0)

COHORT B

<table>
<thead>
<tr>
<th>RT/THAL</th>
<th>Surgery</th>
<th>Post-op Adj. THAL for 6 months Post-op Boost RT if positive margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT/THAL</td>
<td>Surgery</td>
<td>Post-op Adj. THAL for 6 months Post-op Boost RT if positive margin</td>
</tr>
</tbody>
</table>

Cohort B: Neoadjuvant concurrent thalidomide and RT
Continue thalidomide until 1 week prior to surgery Followed by surgical resection and Adjuvant thalidomide for 6 months (post-op boost RT if positive margin; see Section 6.0)

Note: For RT dose and schedule, see Section 6.0; for drug dose and schedule, see Section 7.0; for surgery, see Section 8.0

Required Sample Size: 44 (22 in Cohort A; 22 in Cohort B)
**Patient Population:**

(See Section 3.0 for details.)

The patient must have a primary T2a or T2b (AJCC, 6th ed.) soft tissue sarcoma (STS). The sarcoma must be located on the upper extremity (including shoulder), the lower extremity (including hip), or trunk. Patients with locally recurrent sarcoma are eligible provided there is no evidence of metastatic disease and there has been no prior radiation therapy to the primary site. Tumor ≥ 8.0 cm in maximal diameter and intermediate to high grade, histology grade 3 or 4 for Cohort A; Tumor > 5 cm in maximal diameter and low grade, histology grade 1 or 2 for Cohort B. No evidence of metastatic disease. Men taking thalidomide must use latex condoms every time they have sex with women, since it has been shown that thalidomide can be found in semen or sperm. A female patient of childbearing potential must, in the assessment of the investigators, be reliable in carrying out instructions and be capable of complying with mandatory contraceptive measures as described.
1. Is sarcoma located on upper extremity, lower extremity, or trunk? 
   - (Y)

2. If tumor is high grade 3 or 4, is tumor greater than or equal to 8 cm in greatest dimension? (Cohort A) 
   - (Y/NA)

3. If tumor is low grade 1 or 2, is tumor greater than 5 cm in greatest dimension? (Cohort B) 
   - (Y/NA)

4. Did patient have contrast MRI or contrast CT before biopsy? 
   - (Y)

5. Did patient have histologically confirmed soft tissue tumor biopsy within 8 weeks prior to registration? 
   - (Y)

6. Age greater than or equal to 16? 
   - (Y)

7. Chest CT done within 10 weeks of registration? 
   - (Y)

8. Zubrod 0-1? 
   - (Y)

9. Were all required labs done within 2 weeks of registration? 
   - (Y)

10. ANC greater than 1,500? 
    - (Y)

11. For Cohort A, is the hemoglobin ≥ 8 mg/dL? 
    - (Y/NA)

12. Platelets greater than or equal to 120,000? 
    - (Y)

13. Total Bilirubin less than or equal to 1.5 g/dL? 
    - (Y)

14. Is serum creatinine less than or equal to 1.5 g/dL; and if it is not, is the creatinine clearance greater than 60 ml/min? 
    - (Y)

15. AST and ALT less than or equal to 1.5 X ULN? 
    - (Y)

16. Is the PT and PTT > 1.25 X ULN? 
    - (Y/N)

17. If yes, does the patient take anticoagulants for nonrelated medical conditions such as atrial fibrillation? 
    - (Y)

18. Fibrin split product less than 2 X ULN? 
    - (Y)

19. Fibrinogen greater than 200 mg/dL? 
    - (Y)

20. For Cohort A, heart function EF greater than or equal to 50% and done within 6 months prior to registration? 
    - (Y)

Continued on next page
21. Both male and female patients have agreed to follow all contraceptive requirements and instructions as written in Sections 3.1.5 and 3.1.6 of protocol.

22. Is the patient willing to avoid illegal sedating drugs and alcohol greater than one drink per day?

23. Prior radiation, chemotherapy, or biotherapy for this tumor?

24. Prior thalidomide?

25. Prior investigational agents?

26. Evidence of metastatic disease?

27. History of significant mental illness or medical condition that would preclude patient from undergoing an operative procedure or limit survival to less than two years?

28. Any cardiovascular abnormality resulting in a New York Heart Association Functional Status of greater than or equal to Class II (Appendix II)?

29. Any symptomatic peripheral vascular disease?

30. Any active uncontrolled bacterial, viral, or fungal infection?

31. Currently taking any anti-seizure medications or documented history of uncontrolled seizures?

32. Known history of DVT or pulmonary embolus unrelated to presence of foreign body implants?

33. Known hypercoagulable disorder?

34. Grade 2 or greater fatigue or other global neurocognitive symptomatology?

35. Any known Acquired Immune Deficiency Syndrome?

36. History of uncontrolled myxedema or Grade 3 or greater hypothyroidism?

37. Concurrent or prior malignancies within the last 3 years with the exception of non-invasive malignancies (carcinoma in situ of the cervix, breast, or oral cavity) or squamous or basal cell carcinoma of the skin?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

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

(Continued on next page)
RTOG Institution # _____
RTOG 0330
Case # _____

ELIGIBILITY CHECKLIST (6/22/05)

3. Is the patient eligible for this study?

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

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

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

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

11. Gender

12. Patient’s Country of Residence

13. Zip Code (U.S. Residents)

14. Patient’s Insurance Status

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

16. Treatment Start Date

17. Medical Oncologist

18. Specify grade of tumor: 3-4 (Cohort A) or 1-2 (Cohort B)

19. Tissue/Blood kept for cancer research? (Y/N)

20. Tissue/Blood kept for medical research? (Y/N)

21. Allow contact for future research? (Y/N)

22. Treatment Assignment (A/B)

23. If patient < 18, date study-specific assent was signed.

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

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

Rationale/Hypotheses:
In the United States, there are approximately 8,000 cases of soft tissue sarcomas (STS) diagnosed each year with half of that number dying annually. Retrospective studies have identified tumors that are high grade, larger than 5 centimeters, and located deep to the fascia as factors associated with high risk for recurrence. These factors also predict for greater risk for incomplete surgery or the need for radical surgery including amputation. Large deep sarcomas are generally managed by combined modality treatment of radical surgery and radiation therapy. Most are extremity tumors that often present challenges for limb and function sparing procedures. A high recurrence rate can often be seen in soft tissue sarcomas and treatment has yet to be standardized. Chemotherapy is infrequently used for primary treatment and the clinical problem of multiple local recurrences and eventual metastatic lung disease often confounds ideal outcomes. Thus, these soft tissue sarcomas should serve as an excellent model for the evaluation of new and novel agents and combination therapy and are quite suitable for this proposed trial and evaluation of anti-angiogenic inhibition because of large tumor size and anatomic location with relative superficiality and availability of surgical specimens for histopathologic examination.

Thalidomide is a derivative of glutamic acid and in addition to being classified as an immunomodulating agent, this drug has been shown to have antiangiogenic properties. Clinically, the antiangiogenic activity of this drug has been utilized in a number of trials involving leukemia, metastatic breast cancer, renal cancer, lung cancer, myeloma, glioma, and Kaposi’s sarcoma. Most of these trials involved combination treatment schemes. Data involving in-vivo biologic activity has been sparse but there appears to be a potential relationship to circulating levels of antiangiogenic regulators (bFGF, VEGF) and drug administration. Presently, thalidomide is being intensively investigated with combination chemotherapy for both primary and refractory myeloma, and an NCI trial of adjuvant thalidomide following resection of stage IV colon cancer is ongoing. Although this oral drug is generally well tolerated and may have anti-tumor activity on its own, it seems reasonable to initiate combination therapy schemes for further clinical evaluation of efficacy and biological activity. This is especially important because of the purported cytostatic mechanism of drug action and theoretically there may be synergy between antiangiogenic inhibition and radiation therapy. RTOG has prior experience with radiation therapy/thalidomide for high-grade gliomas and has been able to adequately accrue to these trials.

This concept needs to be further evaluated in a clinical trial on another suitable tumor model. Toxicity of thalidomide-combined therapy as well as the necessity for reliable and reproducible biomarkers also requires further investigation. In addition, RTOG has maturing clinical data and access to archival specimens from a prior neoadjuvant sarcoma trial that can be useful in comparison data analysis for this trial.

Soft tissue sarcomas are ideally suited for trials combining angiogenic inhibitors with radiation and/or chemotherapy. Several studies to date have shown VEGF and bFGF levels to be elevated in patients with soft tissue sarcoma. In one study, VEGF levels were elevated when compared to controls, and elevated pre-treatment VEGF levels correlated with worse survival. In another study of osteosarcoma, pretreatment VEGF levels were significantly elevated in patients with pulmonary metastases, but there was no correlation with bFGF levels. Finally, a third study showed that preoperative serum levels of VEGF and bFGF were elevated in patients undergoing resection of soft tissue sarcoma. This study proposes to evaluate the effects of pre-operative thalidomide combined with either radiation therapy alone or with combination chemotherapy and radiation (depending on tumor grade) on large STS of the extremities or body wall. This study will further evaluate post resectional adjuvant thalidomide in the patients. This study is designed as a phase 2 pilot protocol with the specific objectives of determining feasibility and toxicity of administering thalidomide in this setting and to establish the reproducibility and relevancy of collective data points for response biomarkers. These can be correlated to disease-free survival as surrogate endpoints. Although thalidomide may not be the most efficient therapeutic available for targeting the angiogenic
compartment of the tumor cell/stromal interface, it is an oral agent with antiangiogenic properties and with high patient compliance and tolerability and a relatively low toxicity profile. In addition, there is considerable clinical expertise with its use as a single agent and increasing experience with its use as a combination therapy component. However, as with other types of antiangiogenic treatment there is a paucity of data concerning its in-vivo mechanism of action and its effect on the tumor cell and endothelial cell populations. Presently there are no standards for quantifying angiogenic response and this trial will explore both tissue relevant angiogenic growth elements as well as circulating factors relative to the angiogenic dynamic within solid tumors. The biological correlate investigations as described in Section 10 will use tumor tissue taken at the time of diagnostic biopsy and the time of resection as well as a periodic blood collection scheme to evaluate angiogenic growth factors and circulating endothelial cells. These timed collections will correspond to the treatment schema and will provide data enhancement for these circulating factors for both intra- and inter-patient variability analysis as well as correlation to the fixed tissue markers and the clinical course. The ultimate goal of the RTOG sarcoma effort will be to enhance both local and systemic control by combination therapy in patients with these difficult tumors. This trial should serve as a platform for additional phase 2 sarcoma studies looking toward this model with perhaps another class of specific antiangiogenic therapy. In addition, toxicity will be a carefully monitored component with the goal of decreasing treatment intensity without sacrificing therapeutic efficacy. This trial is already working toward that goal by decreasing the dose density and the total dose of the chemotherapy component by eliminating the post adjuvant chemotherapy. We base this on analysis of data indicating that after neoadjuvant MAID therapy, the post-op adjuvant three cycle MAID regimen in RTOG 95-14 was only completed by 60% of the eligible patients, and 94% of those treated experienced grade 3 or higher hematological toxicity.

2.0 OBJECTIVES

2.1 To assess treatment delivery and toxicity of combination treatment for STS utilizing thalidomide in each patient cohort. For high/intermediate grade, Cohort A, the results will be compared to RTOG 95-14.

2.2 To assess the feasibility of employing specific tissue and circulating biomarkers of antiangiogenic response in a multi-institutional setting.

2.3 To assess quantitative changes and patient variabilities of these biomarkers before, during, and after therapy in each patient cohort.

2.4 To develop baseline data sets of biomarkers particularly circulating endothelial cells for future study design for combined antiangiogenic therapy in this tumor type.

2.5 To assess tolerance of long term post-operative adjuvant thalidomide in each patient cohort.

2.6 To assess clinical response to pre-operative therapy in each patient cohort.

2.7 To assess local control and disease-free survival relative to surrogate biological endpoints in each patient cohort.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 The patient must have a primary T2a or T2b soft tissue sarcoma (AJCC, 6th ed., Appendix III). The sarcoma must be located on the upper extremity (including shoulder), the lower extremity (including hip), or trunk. Patients with locally recurrent sarcoma are eligible provided there is no evidence of metastatic disease and there has been no prior radiation therapy to the primary site. Tumor ≥ 8.0 cm in maximal diameter and Grade 3 or 4 (intermediate to high grade) for Cohort A; Tumor > 5 cm in maximal diameter and Grade 1 or 2 (low grade) for Cohort B.

3.1.2 Age ≥ 16 years; because the long-term effects of thalidomide are not known in patients <16 years of age, children are excluded from this study.

3.1.3 Zubrod performance status must be 0-1.

3.1.4 For Cohort A, normal heart function (study showing EF ≥ 50% within past six months prior to registration). Patients with a history of atherosclerotic coronary artery disease that required bypass surgery may only be enrolled provided that surgery occurred at least one year prior to enrollment and after consultation with a cardiologist to determine stability of disease.
3.1.5 Men taking thalidomide must use latex condoms every time they have sex with women during therapy and for 4 weeks after discontinuing thalidomide, even if they have had a successful vasectomy, since it has been shown that thalidomide can be found in semen or sperm. They should advise their partners with the potential for pregnancy, who may be exposed during the study, to use at least one additional form of birth control. In addition, it is recommended that the women be advised to use one additional form of birth control inclusive of the latex barrier.

3.1.6 A female patient of childbearing potential must meet the following conditions:

3.1.6.1 She must, in the assessment of the investigators, be reliable in carrying out instructions.

3.1.6.2 She must, in the assessment of the investigators, be capable of complying with mandatory contraceptive measures. She must be willing to either abstain from all reproductive sexual intercourse or use 2 methods of birth control: at least 1 highly active method (e.g. intrauterine device [IUD], hormonal [birth control pills, injections, or implants], tubal ligation, or partner’s vasectomy) and 1 additional effective method (e.g. latex condom, diaphragm, or cervical cap) beginning at least 4 weeks before starting thalidomide therapy, during therapy, and for 4 weeks after discontinuing thalidomide therapy. These precautions are mandatory 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.

3.1.6.3 She must receive both spoken and written warnings of the hazards of taking thalidomide during pregnancy as well as the risk of contraception failure and must acknowledge her understanding of these warnings in writing (by signing the informed consent form).

3.1.6.4 Besides the pretreatment pregnancy tests required in Section 3.1.7, all females of childbearing potential must have a negative urine or serum pregnancy test every week during the first 4 weeks of treatment, every 4 weeks while on thalidomide if periods are regular or every 2 weeks if periods are not regular, and at 4 weeks after the last dose of thalidomide.

3.1.7 Pretreatment evaluations required for eligibility include: (6/22/05)

- History and physical with special attention to the size of the primary tumor and including height, weight, body surface (m²), Zubrod.
- For Cohort A patients, MUGA scan or echocardiogram to evaluate LVEF (see Section 3.1.4)
- Radiographic Studies:
  - Contrast enhanced MRI OR contrast enhanced computerized tomography (CT) of primary tumor and extremity prior to biopsy. Contrast enhanced CT is preferable for tumors of the trunk. Tumor size will be measured radiographically using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (See Section 11.2 for details).
  - Pre-operative chest CT must be done within 10 weeks prior to registration. (Patients with overt evidence of lung metastatic disease are excluded from the study; however, because of the sensitivity/specificity of the chest CT, small incidental lesions without a histologic diagnosis may not be a basis for study exclusion.)
- Biopsy: Must be done within 8 weeks prior to registration. Tumor grade must be defined. Grade 1, 2, 3, or 4 to meet eligibility of low, intermediate, or high grade. Open incisional biopsy is preferred; multiple core biopsies under CT or ultrasound guidance are acceptable (with approval of Dr. Eisenberg, Dr. Kraybill, or Dr. Kane) provided they are adequate for demonstration of tumor/stromal interface, open marginal excisional biopsy is acceptable (if measurable disease remains.)
- Laboratory Studies:
  - Must be done within 2 weeks prior to registration; ANC > 1500; platelets ≥ 120,000; total bilirubin ≤ 1.5 mg/dL; serum creatinine ≤ 1.5 g/dL (if >1.5 g/dL, then creatinine clearance should be >60 ml/min); BUN; AST and ALT ≤ 1.5 x ULN; PT and PTT < 1.25 x ULN; Fibrin Split products < 2 x ULN/Fibrinogen >200 mg/dL; electrolytes; glucose; thyroid function tests (TSH, T3, and T4).
- All female patients of childbearing potential must have a negative urine or serum pregnancy test within 48 hours prior to registration and within 24 hours prior to thalidomide administration. Thalidomide will not start until a negative pregnancy test by urine or serum is documented within 24 hours of thalidomide administration.

Pretreatment evaluations must be completed and treatment should begin as soon as possible after registration.

3.1.8 Patients must sign a study-specific informed consent, which includes mandatory use of tissue for central review. If a patient is 16 years or older but not 18 years of age, the patient must sign an assent form, and the permission of at least one parent (preferably both parents) is required. (See Appendices V and VI for a Minor Being Assented.)

3.2 Conditions for Patient Ineligibility (6/22/05)

3.2.1 Any sarcoma of the head, neck, intra-abdominal, or retroperitoneal region.
3.2.2 Prior treatment with radiation, chemotherapy, or biotherapy for this tumor.
3.2.3 Prior treatment with thalidomide.
3.2.4 Patients currently receiving any other investigational agents.
3.2.5 Histopathology demonstrating rhabdomyosarcoma, extraosseous Ewing’s primitive neuroectodermal tumors, osteosarcoma or chondrosarcoma, Kaposi’s sarcoma, angiosarcoma, desmoid tumor, or dermatofibrosarcoma protuberans.
3.2.6 Concurrent or prior malignancies within the last 3 years with the exception of non-invasive malignancies (carcinoma in situ of the cervix, breast or oral cavity) or squamous or basal cell carcinoma of the skin.
3.2.7 Evidence of metastases.
3.2.8 History of a significant medical illness that would preclude the patient from undergoing an operative procedure or limit survival to less than two years.
3.2.9 Patients with uncompensated coronary artery disease on ECG or physical examination, history of myocardial infarction or severe/unstable angina in the past 6 months, uncompensated congestive heart failure, LVEF \( \leq \) 50% (only in Cohort A), or any cardiovascular abnormality resulting in a New York Heart Association Functional Status \( \geq \) Class II. Because of treatment associated symptomatic bradycardia, orthostatic hypotension, syncope, arrhythmias, and sudden death, it is recommended that an EKG and evaluation of any existing cardiac abnormalities be done for all patients to establish a baseline.
3.2.10 Patients with symptomatic peripheral vascular disease.
3.2.11 Active uncontrolled bacterial, viral, or fungal infection until these conditions are corrected or controlled.
3.2.12 Patients who are pregnant while undergoing therapy. There is an extremely high risk that a deformed infant will result if pregnancy occurs while taking thalidomide in any amount, even for a short period of time. All exposed fetuses can be potentially affected.
3.2.13 Documented history of uncontrolled seizures or patients with a history of seizure disorder not well controlled on medication.
3.2.14 Grade \( \geq \) 2 sensory neuropathy based upon the NCI CTCAE, version 3.0, except a localized neuropathy due to a mechanical cause or trauma.
3.2.15 Patients with baseline CTCAE v3.0 grade 2 or greater fatigue or other global neurocognitive symptomatology, taking sedating drugs and cannot reduce these below a minimal level or who will not agree to avoid sedating illegal “recreational” drugs or alcohol greater than one drink per day (as thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine).
3.2.16 Known history of deep vein thrombosis or pulmonary embolus except in patients where the cause was directly related to foreign body implants, i.e. central venous catheters, port-a-caths, etc.
3.2.17 A known hypercoagulable disorder such as APC resistance (factor V Leiden), protein S deficiency, protein C deficiency, antithrombin III deficiency, hyperhomocysteinemia, displasminogenemia, high plasminogen activator inhibitor, dysfibrinogenemia, antiphospholipid syndrome, thrombocythemia, or dysproteinemia.
3.2.18 Any of the following hematologic abnormalities:
Hb < 8.0 gm/dl (Cohort A)
APTT or PT >1.25 X ULN (except in patients who are therapeutically anticoagulated for nonrelated medical conditions such as atrial fibrillation).

3.2.19 A history of hepatic cirrhosis or current hepatic dysfunction with a total bilirubin > 1.5 mg/dl (except for patients with Gilbert’s syndrome who must have a direct bilirubin ≤1.0 mg/dl) or AST/ALT ≥ 2.0 times ULN.

3.2.20 History of uncontrolled myxedema or CTCAE v3.0 grade 3 or greater hypothyroidism.

3.2.21 Renal insufficiency as determined by a serum creatinine >1.5 mg/dl (unless the measured creatinine clearance is > 60 ml/min). (Patients taking any bis-phosphonate may be at a higher risk for renal insufficiency and should be closely monitored.)

3.2.22 Known Acquired Immune Deficiency Syndrome due to reported neurologic side effects (encephalopathy) during treatment with thalidomide.

3.2.23 Inability to give informed consent.

3.2.24 Patients who cannot be regularly followed by the investigator.

3.2.25 Major medical illnesses or psychiatric impairments, which, in the investigator’s opinion will prevent administration or completion of the protocol therapy.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS (6/22/05)
These pretreatment evaluations are recommended in addition to the required eligibility criteria in Section 3.0. A deficiency in these recommended evaluations alone would not lead to patient ineligibility.

4.1 Five blood samples (8 cc each) at various time points including pretreatment for analysis of circulating levels of VEGF and bFGF and circulating endothelial cells sent to Fox Chase Cancer Center (see Section 10.4.3 and Appendix IV)

4.2 EKG

5.0 REGISTRATION PROCEDURES

5.1 Registration

5.1.1 Online Registration (6/22/05)
Online (versus Dial-in) registration is mandatory for this study. Patients can be registered only after eligibility criteria are met. The RA will register the patient by logging onto the RTOG Web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. A username and password is required. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

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

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.
In the event that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, as discussed in Section 5.1.2. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 **RADIATION THERAPY**

6.1 **General Guidelines**

6.1.1 In general, the entire compartment need not be covered. A margin of 5 cm is recommended beyond the gross disease in the longitudinal (proximal and distal) direction. If this causes the field to extend beyond the compartment, the field can be shortened to include the end of the compartment plus a margin of 2 cm. The radial margin from the lesion should be 2 cm including any portion of the tumor not confined by an intact fascial barrier or bone; when an intact fascial barrier or bone is within 2 cm of the tumor, full dose can be placed at the fascial barrier or adjacent bony surface with sufficient margin for any set-up error (generally 0.5 cm).

6.1.2 Scars should be bolused with appropriate thickness specific to energy of photon beam. A wider area of bolus should be used if there is subcutaneous or cutaneous involvement.

6.1.3 Needle biopsy sites should be tattooed or marked so that they can be excised at the time of surgery. This should be done in such a way as to not be confused with the isocenter tattoo.

6.1.4 Every effort should be made to:

a) Avoid treating the full circumference of an extremity.

b) Avoid treating anus, urogenital tract, perineum and genitalia.

c) Avoid treating the lung, through use of appropriate shielding and treatment planning.

d) Avoid dose maximums in areas where surgical scars will be placed. This requires reviewing treatment plans with the surgeon.

e) If possible, avoid treating to full dose, skin over areas commonly traumatized (e.g., the elbow, knee, shin), femoral neck.

6.1.5 Use of CT planning is encouraged if the involved site can be appropriately immobilized and scanned in the CT simulator.

6.1.6 Sparing of a longitudinal strip of skin and subcutaneous tissue is encouraged for at least half of the course, unless adequate radial margins on the tumor as defined above cannot be achieved.

6.1.7 Conventional radiotherapy simulated with a 2-D simulator and conformal radiotherapy planned with a CT simulator are acceptable treatment techniques for this study. Intensity modulated radiation therapy (IMRT) and any form of brachytherapy are not permitted.

6.2 **Preoperative Radiation Therapy**

6.2.1 **Cohort A: Patients receiving MAID chemotherapy**

Treatment is to consist of two courses of external beam radiation therapy (EBRT) interdigitated between MAID courses 1 and 2 and between courses 2 and 3. Each course of EBRT will begin 3 days after completion of each cycle of MAID course (i.e., 2 days off, out of hospital without therapy) and consist of 22 Gy in 11 fractions (once a day) over 15 days. If it falls on a Saturday or Sunday, treatment can resume on Monday. The total preoperative irradiation dose will be 44 Gy in 22 fractions. Thalidomide will be given 7 days per week each evening before bedtime during the radiation phase of the therapy but will not be given concurrent with the chemotherapy.

6.2.2 **Cohort B: Patients not receiving MAID chemotherapy**

Treatment is to consist of 50 Gy in 25 fractions, delivered at 2 Gy per fraction daily over 5 weeks. Thalidomide will be given 7 days per week each evening before bedtime during the radiation phase of therapy.

6.2.3 The target volume of radiation therapy will include the site of the primary lesion and those tissues suspected of involvement by microscopic disease to a clinically important probability. In addition to physical exam findings, MRI scans or CT scans (less desirable) obtained during evaluation will be used in defining the target volume. The longitudinal (proximal and distal) margins beyond clinically or radiologically evident sarcoma will be 5 cm and radial margins will be 2 cm. The radial margin from the lesion should be 2 cm.
around any portion of the tumor not confined by an intact fascial barrier or bone; when an intact fascial barrier or bone is within 2 cm of the tumor, full dose can be placed at the fascial barrier or adjacent bony surface with sufficient margin for any set-up error generally 0.5 cm. Optimal field arrangement, beam parameters and shaped blocks will be used to achieve the closest approximation of treatment volume to target volume to minimize irradiation of uninvolved normal tissue.

6.2.4 Immobilization devices should be used daily to ensure reproducibility of treatment.

6.3 For Patients With Positive Margins: Post-Operative Radiation Therapy in Both Cohorts A and B (given with concurrent thalidomide)

6.3.1 Post-operative external beam radiation therapy (EBRT) boost will be given for patients with positive margins. The radiation treatment is to be completed by administering 16 Gy to the bed of the residual tumor (including a margin of 1 cm). Boost will not be given for patients with 100% necrosis. EBRT will begin approximately 2 weeks following resection, assuming there is satisfactory healing of the surgical wound. At the time of resection, metallic clips will be placed to aid in defining the tumor bed. The target volume for post-operative radiation therapy will be the tumor bed as defined by the operative and pathological findings.

6.3.2 External Beam Post-Operative Boost Guidelines
1) The dose is 16 Gy in 8 fractions (once a day).
2) Bolus can be avoided unless positive margins occur in cutaneous or subcutaneous tissues.
3) It is not necessary to include the entire surgical bed, drain sites, and wound.
4) Surgical staples should remain in place during the boost.

6.4 Dose Specifications
6.4.1 For the two opposed coaxial equally weighted beams: on the central ray at separation of beams.
6.4.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
6.4.3 Any other field arrangement: at the center of the target volume.

6.5 Radiation Adverse Event Reporting (8/17/11)
As of October 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE), version 4 for grading of all adverse events reported via AdEERS. All RTOG case report forms will continue to use CTCAE, v. 3.0. A copy of the CTCAE, v. 4 can be downloaded from the CTEP home page (http://ctep.info.nihcancer.gov), or the RTOG website (http://www.rtog.org/members/toxicity/main.html). Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events. See Sections 7.5 and 7.6 for adverse event reporting requirements.

6.6 R.T. Quality Assurance Reviews
There is no RT Quality Assurance Review planned at this time. In this study, the patient’s sarcoma can be located on the upper extremity (including shoulder), the lower extremity (including hip), or trunk. Since this is a pilot study with a sample size of 22 in each treatment cohort, distinct algorithms for scoring the radiation therapy delivered to the different primary sites would possibly have to be developed for each patient. Instead, the data for the radiation therapy delivered will be collected on each patient as if the data were undergoing final review. Based on the toxicity and/or efficacy results of the study, radiation therapy for selected patients may be reviewed by the Radiation Oncology Co-Chair, Dr. Delaney. These reviews would be performed at RTOG Headquarters.

7.0 DRUG THERAPY
RTOG institutional participation in chemotherapy studies must be in accordance with the medical oncology quality control guidelines stated in the RTOG procedures manual.

Patients in Cohort A will receive a maximum of 3 cycles of neoadjuvant MAID (Mesna, Doxorubicin, Ifosfamide, DTIC) with concurrent thalidomide and radiation therapy. This is followed by surgical resection and adjuvant thalidomide for one year.
Patients registered to Cohort B will receive neoadjuvant concurrent thalidomide and RT followed by surgical resection followed by adjuvant thalidomide for 6 months.

## 7.1 Cohort A (High/Intermediate Grade): MAID/Radiotherapy/Thalidomide

Day 1 of protocol treatment must be a Tuesday.

<table>
<thead>
<tr>
<th>TX</th>
<th>Cycle 1 Days</th>
<th>RT Days</th>
<th>Cycle 2 Days</th>
<th>RT Days</th>
<th>Cycle 3 Days</th>
<th>Surg Day</th>
<th>Post-Op</th>
<th>Adjuvant Thalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesna*</td>
<td>1-4</td>
<td>22-25</td>
<td></td>
<td></td>
<td>43-46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dox</td>
<td>1-3</td>
<td>22-24</td>
<td></td>
<td></td>
<td>43-45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifos</td>
<td>1-3</td>
<td>22-24</td>
<td></td>
<td></td>
<td>43-45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTIC</td>
<td>1-3</td>
<td>22-24</td>
<td></td>
<td></td>
<td>43-45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thal. c</td>
<td>7-21,</td>
<td>28-42</td>
<td></td>
<td></td>
<td>Start Thal. within 2 weeks post-op e</td>
<td>Thal. for 12 months f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>7-21</td>
<td>28-42</td>
<td></td>
<td></td>
<td>80-101 a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>At end of Cycle 1</td>
<td>At end of Cycle 2</td>
<td>At end of Cycle 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td>At end of Cycle 1</td>
<td>At end of Cycle 2</td>
<td>At end of Cycle 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Optional: The same total daily dose of Mesna can be given over 12 hours on day 4 only.
b. 11 treatments in 13-15 days
c. Thalidomide given daily in the evening before bedtime during the radiation therapy phase.
d. For patients with positive margins, 16 Gy (2 Gy x 8 fractions) will be given by external beam (Day 80-101, assuming wound healing is good)
e. Thalidomide given concurrent with post-op RT if boost is necessary.
f. Thalidomide 200 mg/day to 400 mg/day for 12 months post-operatively in patients in Cohort A

### 7.1.1 Pre-operative Chemotherapy

Patients will receive a maximum of 3 cycles of MAID chemotherapy, administered preoperatively, interdigitated with radiation therapy.

#### 7.1.1.1 Mesna: 2500 mg/m²/day as a continuous intravenous infusion administered for 4 days starting on day 1 of the drug cycle and repeated on day 22 and day 43 for 4 days as per protocol (provided patients recovered from their toxicities). See Section 7.4.1 for additional drug information.

Optional: The same dose of Mesna could be given over 12 hours on day 4 only. The daily Mesna dose equals the daily ifosfamide dose and is reduced in parallel if needed.

#### 7.1.1.2 Doxorubicin: 20 mg/m²/day as a continuous intravenous infusion administered via a central line for 3 days starting on day 1 of the drug cycle and repeated on day 22 and day 43 for 3 days (as per protocol)(provided the patients have recovered from their toxicities). See Section 7.4.2 for additional drug information.

#### 7.1.1.3 Ifosfamide: 2500 mg/m²/day as a continuous intravenous infusion for 3 days starting on day 1 of the drug cycle and repeated on day 22 and day 43 for 3 days (as per protocol) (provided the patients have recovered from their toxicities). See Section 7.4.3 for additional drug information.

For those patients who met eligibility despite creatinine >1.5 g/dL by virtue of having a clearance >60 ml/min, use the dose reduction scheme in Section 7.1.3.6.1 to reduce the initial ifosfamide dose.

#### 7.1.1.3.1 Suggested Hydration: Four hours prior to the ifosfamide administration, begin hydration with D5/NS, 2400 cc/day at 100 cc/hr until 6 hours following the completion of the continuous infusion of ifosfamide.

#### 7.1.1.4 DTIC: 225 mg/m²/day as a continuous intravenous infusion administered via a central line for 3 days starting on day 1 of the drug cycle and repeated on day 22 and day 43 for
3 days (as per protocol) (provided patients have recovered from their toxicities). See Section 7.4.4 for additional drug information.

7.1.1.5 Drug Mixing
Both mesna and ifosfamide can be mixed together in one liter D5W and administered via peripheral line. Both doxorubicin and DTIC can be mixed together in 1 liter NS and administered via a central line (should be protected from light).

7.1.1.6 G-CSF: Filgrastim (Neupogen®) OR Pegfilgrastim (Neulasta®) [10/18/05]
Filgrastim (Neupogen®), 5 mcg/kg/day administered as a subcutaneous injection starting on day 5 (24 hours after completion of the administration of the chemotherapy) and continuing daily until white blood cell count recovers (post nadir granulocyte or ANC count of >10,000) even if the G-CSF is given concurrently with the radiation therapy. While the patients are receiving G-CSF, white blood cell counts and differential counts should be checked at least twice weekly until the G-CSF is discontinued.

Pegfilgrastim (Neulasta®), 6 mg (fixed dose regardless of weight) administered as a subcutaneous injection x 1 on day 5 only (24 hours after completion of the administration of the chemotherapy). See Section 7.4.5 for additional drug information.

7.1.2 Drug Dose Modification
The doses of chemotherapy will be attenuated as follows. The most severe toxicity should determine the degree of attenuation.

7.1.2.1 Hematology Toxicity [10/18/05]
Ifosfamide (and Mesna in parallel), Doxorubicin and DTIC doses are to be modified based both on the nadir (day 14) counts of the previous cycle and counts obtained on the day treatment is given. No new treatment course may begin unless the patient’s granulocyte count is > 1500/ml and platelet count is > 100,000/ml. If these are not present on day 22, then repeat counts weekly; if after 2 weeks the patient’s counts are not adequate for therapy, contact Drs. Harmon or Ettinger.

<table>
<thead>
<tr>
<th>Absolute Neutrophil Count (Reduce doses only if ANC is &lt; 1000 for &gt; 5 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC Nadir of Last Course</td>
</tr>
<tr>
<td>&gt; 1000</td>
</tr>
<tr>
<td>500-1000</td>
</tr>
<tr>
<td>&lt; 500</td>
</tr>
</tbody>
</table>

If the patient has an ANC < 1000, the CBC should be repeated 3 times weekly until the ANC is > 1500. There will be a dose reduction only if the ANC remains below 1000 for greater than 5 days.

<table>
<thead>
<tr>
<th>Platelets Nadir of Last Course</th>
<th>Plus Platelets of &gt; 100,000 on Day 1 of each cycle</th>
<th>% Dose to Give</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 75,000</td>
<td>(Note: Platelets of ≤ 100,000 on Day 1 = Hold until platelets &gt; 100,000)</td>
<td>100%</td>
</tr>
<tr>
<td>50,000-75,000</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>&lt; 50,000</td>
<td></td>
<td>70%</td>
</tr>
</tbody>
</table>

In the event that dose adjustments are needed for both ANC and platelets, patients are to receive the lower dose.

Treatment should be delayed for one week until ANC is > 1500, and the platelet count is >100,000. If after one week the counts have recovered, the patient should proceed with the next course of treatment (Day 1) based on the previous course’s nadir counts. However, if the counts have not recovered in two weeks, contact Dr. Harmon or Dr.
Ettinger. Patients and investigators need to be attentive to the possibility of fever and infection so that these complications can be promptly and appropriately managed.

When a dose reduction is made for a decreased ANC or platelet count and the reduced dosage results in no toxicity, the next course should be given at intermediate-dose rather than full-dose, e.g., if a 30% dose reduction results in no toxicity, the next course should start at 80% dose rather than 100% (i.e. 70% dose increased to 80% of dose, and 80% dose would be increased to 100%).

Dose reductions are not based on a single nadir count. The ANC must remain < 1,000 for > 5 days before a dose reduction is made. If chemotherapy must be withheld due to hematologic toxicity, CBC and platelet counts should be obtained weekly until the counts reach the lower limits of treatment as outlined. The treatment schedule will then proceed in the usual sequence.

7.1.2.2 Gastrointestinal Toxicity (Ifosfamide, Doxorubicin, DTIC)
Nausea and/or vomiting should be controlled with adequate antiemetics. If grade 3 or greater nausea/vomiting occurs in spite of antiemetics, the dose should be reduced by 30% for the next course. If tolerated, increase back to 100% dose as soon as possible. If the toxicity recurs, reduce the dose by 30%. If toxicity returns at this dose, discontinue drug.
If on Day 1 of any treatment cycle the patient has mucositis, the treatment should be withheld until the mucositis is cleared completely. If acute grade 3 mucositis occurs at any time, the dose should be given at 75% dose until the mucositis is completely cleared. Drug can be given at full dose for subsequent cycles.

7.1.2.3 Hepatic Toxicity
Give the following percent of previous course’s dose based on the patient’s bilirubin the day of treatment. Dose limiting toxicity (DLT) for the purposes of this study will be defined as Bilirubin > 3.0 - < 5.0 mg/dl. Drug is held until resolution of the DLT to baseline, at which time drug is restarted at the next lowest dose level.

<table>
<thead>
<tr>
<th>Liver Function Test Result</th>
<th>% Agent to Give</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>≤ 1.5</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 1.5 - &lt; 3.0</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 3.0 - &lt; 5.0</td>
<td>25%</td>
</tr>
<tr>
<td>5.0</td>
<td>0%</td>
</tr>
</tbody>
</table>

7.1.2.4 Neurotoxicity
Ifosfamide doses will be modified for neurotoxicity as outlined below:

7.1.2.4.1 Mild Somnolence Grade 2 by CTCAE 3.0 not interfering with ADL (sleeping constantly but easily aroused and oriented): Decrease dose of narcotics or antiemetics; continue ifosfamide with no change in dose.

7.1.2.4.2 Moderate Somnolence Grade 3 by CTCAE 3.0 interfering with ADL (difficult to arouse or disoriented when finally awakened): discontinue Ifosfamide until toxicity clears and then reinstitute at same dose. If moderate somnolence recurs, again discontinue Ifosfamide and reinstitute at 25% dose reduction for the rest of the course. If the same symptoms recur at the reduced dose, again hold until symptoms resolve and restart at a 25% further dose reduction. If symptoms recur after a 50% reduction, discontinue permanently.

7.1.2.4.3 Visual Hallucinations, Confusion, Catatonia Grade 2 Psychosis by CTCAE 3.0
Hold Ifosfamide, reinstate at 25% reduced dose with next course, minimizing any other psychoactive medications. If symptoms recur, decrease Ifosfamide dose by another 25% with the subsequent course. If symptoms recur after a 50% dose reduction, discontinue permanently.
7.1.2.5 **Cardiovascular Toxicity**
Cardiac Events: Doxorubicin should be withheld if EKG abnormalities or congestive heart failure develops. Non-invasive ventricular function studies should be performed if available. If EKG abnormalities improve, Doxorubicin may be reinstituted, but it should not be reinstituted if congestive heart failure or ventricular dysfunction are present. Patients whose MUGA scan drops to less than 50% should be removed from the study.

7.1.2.6 **Genitourinary**
Cystitis: Ifosfamide-related gross or microscopic hematuria correlates with the concentration of drug metabolites in the bladder. Adequately hydrate patients, and ensure frequent voiding. Should grade 2 hemorrhagic cystitis occur, discontinue Ifosfamide. Reinstitute Ifosfamide at a 50% reduced dose when hematuria has cleared. If grade 2-3 bladder toxicity occurs at the 50% dose reduction, discontinue Ifosfamide permanently. Ifosfamide may be escalated to full dose after dose reduction with subsequent courses if no hematuria occurs at the 50% dose reduction.

7.1.2.6.1 **Nephrotoxicity**
Give the following percent of the previous course’s dose for nephrotoxicity based on renal function on the day of treatment.

<table>
<thead>
<tr>
<th>Serum Creatinine</th>
<th>Doxorubicin</th>
<th>DTIC</th>
<th>Ifosfamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5 mg/dl</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 – 2.0 mg/dl</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>2.1 – 3.0 mg/dl</td>
<td>100%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 3.0 mg/dl</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

7.1.2.7 **Miscellaneous Toxicity**
7.1.2.7.1 Skin Ulceration/Phlebitis: Doxorubicin may cause chemical phlebitis, even when administered by continuous infusion through side-arm of a rapidly running intravenous infusion. Chemical phlebitis is not an indication to stop any drug. Doxorubicin must be administered through central line (*not merely a long line*).

7.1.2.7.2 Extravasation outside a vein will cause skin necrosis; stop the infusion immediately if extravasation is suspected.

7.1.2.7.3 Fever and Flu-like Syndrome associated with DTIC administration may be avoided with oral acetaminophen.

7.1.2.7.4 Alopecia: Ifosfamide and Doxorubicin cause total alopecia.

7.1.2.7.5 For any grade 3 or 4 toxicity not mentioned above, the treatment should be withheld until the patient recovers completely or to grade 1 toxicity. The treatment should then be resumed at 50% dose (permanent dose reduction). For grade 1 or 2 toxicities, no dose reduction should be made.

7.1.3 **Thalidomide (Cohort A, high/intermediate grade) [4/20/06]**
Note: If no contraindication, add daily 81 mg ASA each morning on same days as thalidomide.

At the beginning of the pre-op radiotherapy phase, the patients will also begin thalidomide at 200 mg/day. The thalidomide will be given daily 7 days per week in the evening before bedtime during the radiation therapy phase. (Dose modification in Section 7.1.3.1)

Patients will NOT TAKE thalidomide during the MAID chemotherapy.

Two weeks after surgery or when the post-op radiotherapy begins (for the subset who need radiation boost for positive margins) resume thalidomide at 200 mg/day (or at the last well-tolerated dose). The post-op thalidomide will be administered daily for one year regardless of the boost radiation schedule.

Physicians must document the patient’s use of all home oral medications at each check-up. They should note whether patients have kept up a diary to corroborate their self-reporting.
If the patients are not having any neuropathy, they will have the option to escalate up to 400 mg/day post-operatively.

They will continue thalidomide until one year from the first dose of post-op thalidomide with dose modifications as in Section 7.1.3.1.

### 7.1.3.1 Thalidomide Dose Modifications:

**If the patient becomes PREGNANT, STOP THALIDOMIDE.**

If the patient remains bed-bound, hold thalidomide until again ambulatory.

If no greater than grade 1 toxicity has been seen, then post-op the standard 200 mg/day may be escalated up to 400 mg/day (for the high risk Cohort A only).

Escalation can be at any rate agreed by the treating physician and patient but to a maximum dose of 400 mg/day.

Dose modification for grade 2 peripheral neuropathy, fatigue, bradycardia, orthostatic hypotension, brady or tachyarrhythmia should be a 50% dose reduction without escalation after resolution. Any rash grade 2 or greater should require holding drug until an evaluation for serious dermatologic reactions including erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome has been done. In addition to depression, several instances of dissociative behavior have been reported. Please hold thalidomide pending evaluation for evidence of changes in behavior that may be associated with the agent. All other grade 2 events should require holding drug until resolution to less than grade 2 and may be restarted. Patients with DVT, seizures, or any grade 3 toxicity should have drug held until resolution less than or equal to grade 1, adequate therapeutic control, and restarted at a 50% dose reduction, without escalation. Patients with non-hematologic grade 4 toxicity should be taken off treatment with investigational agent.

If grade 4 neutropenia is encountered at any point in therapy, the thalidomide must be held until recovery to less than grade 3.

### 7.2 Cohort B (Low Grade): RT/Thalidomide

<table>
<thead>
<tr>
<th>TX</th>
<th>RT Days</th>
<th>Thalidomide</th>
<th>Surg Day</th>
<th>Post-Op</th>
<th>Adjuvant Thalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thal.</td>
<td>1-35 during RT</td>
<td>Start day 36 and stop 1 week prior to surgery</td>
<td>Start Thal. within 2 weeks post-op&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Thalidomide for 6 months&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>1-35</td>
<td></td>
<td>May start 2 weeks after surgery once wound healed&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>77-91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. For patients with positive margins, 16 Gy (2 Gy x 8 fractions) will be given by external beam (Day 91, assuming wound healing is good)
b. Thalidomide given daily in the evening before bedtime concurrent with post-op RT if boost is necessary.
c. Thalidomide 200 mg/day for 6 months post-operatively for patients in Cohort B start 2 weeks post-op

**7.2.1** Pre-op thalidomide 200 mg/day is added to pre-op radiotherapy. (Dose modifications in Section 7.2.3.) Thalidomide is given daily 7 days per week in the evening before bedtime during the radiation therapy phase. If no contraindication, add daily 81 mg ASA in the morning on same days as thalidomide.
Physicians must document the patient’s use of all home oral medications at each check-up. They should note whether patients have kept up a diary to corroborate their self-reporting.

7.2.2 Resume 2 weeks post-op and continue daily for a total of 6 months of thalidomide with no dose escalation. If post-op RT boost is given, thalidomide will be administered with the RT. If no contraindication, add daily 81 mg ASA in the morning on same days as thalidomide.

7.2.3 **Thalidomide Dose Modifications:**
If the patient becomes PREGNANT, STOP THALIDOMIDE.
If patient remains bed-bound, hold thalidomide until again ambulatory.

There will be no dose escalations for Cohort B.

Dose modification for grade 2 peripheral neuropathy, fatigue, bradycardia, orthostatic hypotension, brady or tachyarrhythmia should be a 50% dose reduction without escalation after resolution. Any rash grade 2 or greater should require holding drug until an evaluation for serious dermatologic reactions including erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome has been done. In addition to depression, several instances of dissociative behavior have been reported. Please hold thalidomide pending evaluation for evidence of changes in behavior that may be associated with the agent. All other grade 2 events should require holding drug until resolution to less than grade 2 and may be restarted. Patients with DVT, seizures, or any grade 3 toxicity should have drug held until resolution less than or equal to grade 1, adequate therapeutic control, and restarted at a 50% dose reduction, without escalation. Patients with non-hematologic grade 4 toxicity should be taken off treatment with investigational agent.

If grade 4 neutropenia is encountered at any point in therapy, the thalidomide must be held until recovery to less than grade 3.

7.3 **Thalidomide (Thalomid®)**
For further information on thalidomide, refer to the package insert.

7.3.1 **Formulation:** THALOMID® (thalidomide), a-(N-phthalimido) glutarimide, is an immunomodulator agent. The empirical formula for thalidomide C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub> and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1. Thalidomide is an off-white to white, nearly odorless, crystalline powder that is soluble at 25° C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S(-) and R(+), forms and, therefore, has net optical rotation of zero. Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

7.3.2 **Availability:** Thalidomide is supplied by NCI as 50 mg hard gelatin capsules (size 0) containing an off-white to white, nearly odorless and crystalline powder. The capsules are imprinted with “Celgene” and a “do not get pregnant” logo.

7.3.3 **Pharmacokinetics:** Clinical pharmacokinetics studies have shown that thalidomide when administered as a single 200-mg dose, the mean peak plasma concentration is 1.9 µg/ml ± 0.5, occurring 3.3 hours ± 1.7 after dosing. Mean half-life of elimination is 5.9 hours ± 2.1. Single dose, dose proportionality was evaluated over the clinical dose range, i.e., from 50 to 400 mg. The extent of absorption is proportional to dose; however, as the dose increases beyond 200 mg, a flattening of the peak concentration is seen with a delay in the time of the peak concentration. The mean peak plasma concentration following a single 400 mg dose administration was 2.82 µg/ml ± 0.80 occurring by 4.3 ± 1.6 hours after the dose; mean half-life of elimination was 7.29 hours ± 2.62. The rate of absorption was also slower at the highest dose as evidenced by a rate constant of absorption that was approximately one-half that observed at the lower doses.

7.3.4 **Storage and Stability:** Thalidomide has been shown to be stable for up to 24 months when stored under ambient conditions. Over this time period, the capsules show no significant
loss in potency and no increase in degradation products. Thalidomide has been shown also to be stable when stored under accelerated conditions (40°C /75% Relative humidity, 3 months). Clinical supplies should be retained in a secure, cool dry place.

7.3.5 (6/22/05) Accountability and Supply: The Principal Investigator (or authorized designee, who the investigator has listed on their most recent Supplemental Investigator Data Form (IDF) on file with the PMB) at each participating institution may request thalidomide, from NCI’s Pharmaceutical Management Branch (PMB). PMB will not provide drug to a site until the site has registered the patient. The updated version (11/10/03) of each institution’s Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the investigator during the annual investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes necessary to this information will require updating the first two pages of the IDF, having been signed by the investigator, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time. 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.

7.3.6 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).

7.3.7 Route of Administration: Oral

7.3.8 Side Effects/Toxicity: (6/22/05)

The Comprehensive Adverse Events and Potential Risks List (CAEPR) for Thalidomide (NSC #66847)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. This subset of AEs (ASAEL) contains events that are considered ‘expected’ for expedited reporting purposes only. Refer to the “CTEP, NCI Guidelines: Adverse Event Reporting Requirements” http://ctep.cancer.gov/reporting/adeers.html for further clarification. The CAEPR does not provide frequency data; refer to the Investigator’s Brochure for this information. Below is the CAEPR for Thalidomide.

<table>
<thead>
<tr>
<th>Category (Body System)</th>
<th>Adverse Events with Possible Relationship to Thalidomide (CTCAE v3.0 Term)</th>
<th>“Agent Specific Adverse Event List” (ASAEL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td></td>
</tr>
<tr>
<td>BLOOD/BONE MARROW</td>
<td>Leukocytes (total WBC)</td>
<td>Leukocytes (total WBC)</td>
</tr>
<tr>
<td></td>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
</tr>
<tr>
<td>CARDIAC ARRHYTHMIA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sinus bradycardia

**CARDIAC GENERAL**

Hypotension

**CONSTITUTIONAL SYMPTOMS**

Fatigue (asthenia, lethargy, malaise)

**DERMATOLOGY/SKIN**

Dry skin

Pruritus/itching

Rash/desquamation

Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)

**ENDOCRINE**

Thyroid function, low (hypothyroidism)

**GASTROINTESTINAL**

Constipation

Dry mouth/salivary gland (xerostomia)

Heartburn/dyspepsia

Nausea

**LYMPHATICS**

Edema:limb

**METABOLIC/LABORATORY**

ALT, SGPT (serum glutamic pyruvic transaminase)

AST, SGOT (serum glutamic oxaloacetic transaminase)

**MUSCULOSKELETAL/SOFT TISSUE**

Muscle weakness (not due to neuropathy) - Select

**NEUROLOGY**

Confusion

Dizziness

Mood alteration: depression

Neuropathy: motor

Neuropathy: sensory

Seizure

Somnolence/depressed level of consciousness

Tremor

**OCULAR/VISUAL**

Dry eye syndrome

Vision-blurred vision

**PAIN**

Pain - head/headache

Pain - muscle

**PULMONARY/UPPER RESPIRATORY**

Dyspnea (shortness of breath)

**SEXUAL/REPRODUCTIVE FUNCTION**

Sexual/Reproductive Function - Other (Teratogenic effects - birth defects)

**VASCULAR**

Peripheral arterial ischemia

Thrombosis/thrombus/embolism

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Version 1.0, March 8, 2005
This table will be updated as the toxicity profile of the agent is revised. Updates will be
distributed to all Principal Investigators at the time of revision. The current version can be
obtained by contacting ADEERSMD@tech-res.com. Your name, the name of the
investigator, the protocol and the agent should be included in the e-mail.

Also reported on Thalidomide trials but with the relationship to Thalidomide still
determined: allergic rhinitis; hemoglobin; platelets; splenic function; atrial fibrillation; atrial
flutter; palpitations; supraventricular tachycardia; cardiac ischemia/infarction; fever;
insomnia; rigors/chills; sweating; weight gain; weight loss; sudden death; acne; alopecia;
hand-foot skin reaction; nail changes; ulceration; anorexia; diarrhea; flatulence; pharyngeal
mucositis/stomatitis; vomiting; respiratory tract hemorrhage; urinary hemorrhage; liver
dysfunction/failure; pancreatitis; febrile neutropenia; HIV viral load increase; opportunistic
infection; head/neck edema; lymphadenopathy; acidosis; albuminuria; alkaline
phosphatase; creatinine; hyperglycemia; hyperlipemia; lipase; neck rigidity; agitation;
anxiety; apnea; ataxia; CNS ischemia; paranoia; psychosis; speech impairment; suicide;
syncope; abdominal pain; back pain; bone pain; dental pain; joint pain; limb pain; neck
pain; cough; pleural effusion; renal failure; infertility/sterility; flu-like syndrome.

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

Additional adverse events reported in Celgene-sponsored controlled clinical trials: chills,
fever, diaphoresis, acne, dermatitis fungal, skin ulcers, nail disorder, pharyngitis, back pain,
neck pain, neck rigidity, pain, flatulence, anemia, lymphadenopathy, hepatic failure,
hyperlipemia, agitation, insomnia, nervousness, hallucinations, paranoia, infection,
sinusitis, oral moniliasis, albuminuria, hematuria, and impotence.

Please refer to the commercial package insert for a comprehensive list of other
adverse events that have been observed in HIV-seropositive patients participating in
uncontrolled clinical trials.

Potential Drug Interactions:

Thalidomide has been reported to enhance the sedative activity of barbiturates,
alcohol, chlorpromazine, and reserpine.

Medications known to be associated with peripheral neuropathy should be used with
cautions in patients receiving thalidomide.

Available data from three clinical pharmacology studies sponsored by Celgene Corporation
showed that 38 patients have been exposed to single doses of thalidomide given either on
one occasion or three occasions with one or two week washouts between doses. Two
studies were conducted in healthy volunteers and the third study was conducted in patients
with Hansen’s disease. Thalidomide was administered in a 50 to 400 mg single dose
range.

Based on the results of the studies, the most frequently reported adverse experiences were
dizziness (31 patients or 82%), somnolence (29 patients or 76%), headache (15 patients or
39%), and asthenia (12 patients or 32%). Somnolence and dizziness were reported to
occur more frequently at doses of 200 mg and 400 mg than they did at a dose of 50 mg.
There was no dose relationship evident for the remaining adverse experiences.

There was no reported severity in intensity of all adverse events. All events were mild
with the exception of moderate somnolence in 13 patients, moderate dizziness in 6
patients, moderate headache in 4 patients, moderate hypotension in 2 patients and
moderate constipation and moderate pallor in 2 patients, and a single report of moderate asthenia, diarrhea, leg cramps, nausea and rhinitis.

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common and potentially severe side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following short-term use also exist. The correlation with cumulative dose is unclear. Patients should be examined at monthly intervals for the first three months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling, or pain in the hands and feet. Patients should be evaluated periodically every 3 months thereafter during treatment.

Serious dermatologic reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, which may be fatal, have been reported in association with thalidomide therapy. Thalomid® should be discontinued if a skin rash occurs, and only resumed following appropriate clinical evaluation. If the rash is purpuric, vasculitic, exfoliative, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of Thalomid® should not be resumed.

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.

Other general side effects include constipation, headache, nausea, xerostomia, loss of libido, increased appetite, weight gain, facial edema, galactorrhea, leucopenia, menstrual abnormalities, alopecia, eosinophilia, and depression.

Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID® (thalidomide) in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

This medicine is for patient use ONLY. IT SHOULD NOT BE SHARED WITH ANYONE. It should be safely stored and be kept out of reach of children.

Do not drink alcohol or take any other medicine that has not been prescribed by the doctor, especially nonprescription drugs that make the patient sleepy as thalidomide may cause drowsiness and intensify this effect.

Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide.

7.3.9 WARNING

Women

THALOMID® (thalidomide) can cause severe birth defects in humans. Women of childbearing potential must confirm to the best of their knowledge that they are not pregnant nor intend to become pregnant during the study. The doctor must give the patient a pregnancy test (sensitivity of at least 50 mIU/mL) performed within 24 hours of beginning thalidomide. If the patient is pregnant, she cannot take thalidomide. Women of childbearing potential must use adequate contraception methods (oral birth control pills, IUD, or depo provera) during their participation in the study. Barrier methods
alone (i.e. condoms) are not sufficient. **The patient must use at least one highly effective method and one additional method AT THE SAME TIME.** However, the doctor may recommend that the patient use two barrier methods for medical reasons.

These birth control methods must be used for at least 4 weeks before starting thalidomide therapy, all during thalidomide therapy, and for at least 4 weeks after thalidomide therapy has stopped.

The patient must talk to the doctor before changing any birth control methods she has already agreed to use.

The following are acceptable birth control methods:

<table>
<thead>
<tr>
<th>Highly Effective Methods</th>
<th>Additional Effective Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine device (IUD)</td>
<td>Latex condom</td>
</tr>
<tr>
<td>Hormonal (birth control pills, injections, implants)</td>
<td>Diaphragm</td>
</tr>
<tr>
<td>Partner’s vasectomy</td>
<td>Cervical Cap</td>
</tr>
</tbody>
</table>

The patient must have pregnancy tests before and during treatment, even if she agrees not to have reproductive heterosexual intercourse. The patient must have a pregnancy test done by the doctor **every week** during the first 4 weeks of treatment. She must have a pregnancy test **every 4 weeks** if her menstrual cycles are regular or **every 2 weeks** if her cycles are irregular. The patient may also need to have a pregnancy test if she misses her period or has unusual menstrual bleeding.

If the patient has sex without birth control or if for any reason thinks she may be pregnant, she must IMMEDIATELY stop taking thalidomide and notify the study investigator.

Women of childbearing potential should not handle or administer thalidomide unless they are wearing gloves. It is unknown whether thalidomide powder is absorbed through the skin. The teratogenic risks associated with cutaneous exposure have not been quantified. Intact capsules are cleaned after manufacture to remove any residual powder and should provide a sufficient barrier to prevent skin contact with the powder. Opening the capsules and removing the capsule contents may increase the risk of cutaneous exposure to thalidomide. Thalidomide does not induce abortion of the fetus and should never be used for contraception.

The patient must be informed and understand the risk of birth defects and agree not to become pregnant while taking thalidomide. The patient must not breast-feed a baby while she is being treated with thalidomide.

The patient must NEVER donate blood or ova while she is being treated with thalidomide.

**Men**

The patient must be informed and understand the risk of birth defects and must agree to NEVER have sex with a woman unless he uses a latex condom while he is taking thalidomide and for 4 weeks after he stops taking the drug, even if he has had a successful vasectomy. He should advise partners with the potential for pregnancy and who may be exposed during the study, to use at least one additional form of birth control.

The patient must tell the doctor if he has sex with a woman without using a latex condom, or if he thinks for any reason that his partner may be pregnant.
The patient must NOT be a sperm or blood donor while he is being treated with thalidomide.

### 7.4 Additional Chemotherapy Drug Information

#### 7.4.1 Mesna (Mesna)
For further information on mesna, refer to the package insert. (7/21/04)

- **Dose Formulation:** Mesna is available as an injectable sterile preservative-free aqueous solution. The colorless solution is supplied in clear glass ampoules containing 10 ml multiple dose vials. Mesna may be further diluted in 5% dextrose, 5% dextrose and 0.45% normal saline or normal saline. Mesna should be given as a continuous intravenous infusion via peripheral line.

- **Mechanism of Action:** Mesna is an uroprotective agent used to prevent hemorrhagic cystitis induced by the oxasphosphorines (Ifosfamide, cyclophosphamide). It has no intrinsic cytotoxicity, no antagonistic effect on radiotherapy or chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by the oxasphosphorines to produce a non-toxic thioether, and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxasphosphorines.

- **Drug Availability:** Mesna is commercially available in 10 ml multiple dose vials.

- **Storage:** Intact ampoules are stored at room temperature. Diluted solutions are physically and chemically stable for 24 hours under refrigeration.

- **Side Effects:** At the doses used for uroprotection, mesna is virtually non-toxic. However, adverse effects that have been attributable to mesna include: nausea, vomiting, diarrhea, abdominal pain, rash, lethargy, headache, arthralgia, myalgias, fatigue, and bad taste in mouth.

#### 7.4.2 Doxorubicin (Adriamycin, Rubex)
For further information on doxorubicin, refer to the package insert.

- **Dose Formulation:** Doxorubicin is available as a red powder for injection in 10, 20, 50, 100, and 150 mg vials. Add 5, 10, 25, 50, or 75 ml of preservative-free normal saline to the 10, 20, 50, 100, or 150 mg vials respectively to produce a solution containing 2 mg/ml. Doxorubicin should be given as a continuous intravenous infusion via a central line.

- **Mechanisms of Action:** Doxorubicin is an anthracycline antibiotic. It causes intercalation between adjoining nucleotide pairs in the DNA helix causing inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

- **Drug Availability:** Doxorubicin is commercially available.

- **Storage:** Adriamycin RDF or Rubex intact vials are stable if protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

- **Side Effects:**
  - **Hematologic:** Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.
  - **Dermatologic:** Alopecia, usually complete; hyperpigmentation of nail beds and dermal creases; radiation recall. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia; diarrhea; mucositis, especially with daily x 3 schedule.
  - **Cardiovascular:** Arrhythmias, ECG changes; rarely, sudden death. Congestive heart failure due to mediastinal irradiation pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.
  - **Other:** Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity.
  - **Local effects:** Vesicant if extravasated; flush along vein, facial flush.

#### 7.4.3 Ifosfamide (Iflex)
For further information about ifosfamide, refer to the package insert.

- **Dose Formulation:** Ifosfamide is available as a white crystalline powder in 1 and 3 gram single dose vials. When the 1 and 3 gram vials are reconstituted with 20 and 60 ml of sterile water respectively, each vial will contain 50 mg/ml. The solution's pH is
approximately 6. Ifosfamide should be given as a continuous intravenous infusion via a peripheral line.

7.4.3.2 Mechanism of Action: Ifosfamide is an alkylating agent, which is activated by hepatic microsomal enzymes to reactive alkylating substance. The reactive metabolites, ifosfamide mustard and aldophosphamide, are capable of covalent binding and cross-linking of DNA and cellular proteins.

7.4.3.3 Drug Availability: Ifosfamide is commercially available.

Storage: If reconstituted with bacteriostatic water for injection, the sterile reconstituted solution is stable for 1 week for 30-C or 3 weeks at 5-C. Ifosfamide liquefies at temperatures above 35-C.

7.4.3.4 Side Effects:
Hematologic: Leukopenia, thrombocytopenia (dose-limiting); anemia.
Dermatologic: Alopecia, rash, urticaria.
Gastrointestinal: Nausea, vomiting, anorexia, constipation, diarrhea, salivation, stomatitis.
Hepatic: Elevated SGOT and SGPT, hyperbilirubinemia.
Genitourinary: Hemorrhagic cystitis (incidence related to dose and schedule; more common with a single high dose); elevated creatinine.
Neurologic: Somnolence, lethargy, disorientation, confusion, dizziness, malaise.
Other: Hyponatremia, hypokalemia, phlebitis, fever, hypo- or hypertension.

7.4.4 Dacarbazine (DTIC) For further information on dacarbazine, refer to the package insert.

7.4.4.1 Dose Formulation: The drug is available in vials containing 100 mg, 200 mg, or 500 mg of lyophilized drug. The 100, 200, and 500 mg vials are diluted with 9.9, 19.7, and 49.5 ml of sterile water respectively, resulting in a concentration of 10 mg/ml. Protect the drug from direct light. Do not freeze. Discard if the solution turns pink/red. The drug can be further diluted in 50-500 ml of 5% dextrose and normal saline. DTIC should be given as a continuous intravenous infusion via a central line.

7.4.4.2 Mechanism of Action: DTIC is classified as an alkylating agent. Activity may be the result of at least 3 mechanisms: (1) alkylation; (2) antimetabolite activity as a purine precursor; and (3) interaction with sulfhydryl (SH) groups in proteins. Dacarbazine appears to be more active in G2 phase but is not particularly cell cycle phase specific.

Drug Availability: DTIC is commercially available.

7.4.4.3 Storage: Store vials under refrigeration and protected from light. In solution, dacarbazine is stable for 96 hours if refrigerated and protected from light, 24 hours if not refrigerated but protected from light. When further diluted in 500 ml D3W or NS, it is stable for 24 hours if refrigerated, and 8 hours at room temperature and protected from light.

7.4.4.4 Photodegradation: The manufacturer of dacarbazine states that the drug does not decompose when left at room temperature under normal room lighting conditions for eight hours. Please protect from direct sunlight.

Note: A change in color of solution from pale yellow to pink is indicative of decomposition of the drug.

7.4.4.5 Incompatibility: Metabolism of dacarbazine may be inducted by phenytoin or phenobarbital. Toxicity may be enhanced if given concomitantly with allopurinol, azathioprine, or mercaptopurine. Dacarbazine is physically incompatible with hydrocortisone sodium succinate and heparin.

7.4.4.6 Side Effects:
Hematologic: Myelosuppression; nadir of WBC and platelet depression occurs approximately 21-25 days of treatment.
Dermatologic: Alopecia; facial flushing; extravasation may result in severe pain but has not resulted in tissue damage. Rapid i.v. push may result in pain along injection site or thrombophlebitis.
Gastrointestinal: Severe nausea and vomiting which characteristically lessen with each subsequent daily dose.
Hepatic: Increased SGOT, SGPT.
Renal: Increased serum creatinine, BUN.
Neurologic: Facial paresthesia.
Other: Flu-like syndrome (with fever, malaise, myalgia) rarely occurs approximately about 7 days after treatment and lasts 1-3 weeks. Rarely, anaphylaxis.

7.4.5 G-CSF – Filgrastim (r-methHuG-CSF, Neupogen®) [10/18/05]

NOTE: Refer to the commercial package labeling for full prescribing information.

7.4.5.1 Dose-Formulation: Commercial Neupogen® is available in 1 ml and 1.6 ml vials at a concentration of 300 mcg/ml. Discard unused portions. Use only one dose per vial; do not re-enter the vial. Do not save unused drug for later administration. Neupogen® is also available as single-dose, preservative-free, pre-filled syringes with 26 gauge, 5/8 inch needles containing 300 mcg (0.5 ml) of Filgrastim (600 mcg/ml) and 480 mcg (0.8 ml) of Filgrastim (600 mcg/ml).

7.4.5.2 Mechanism of Action: Filgrastim is a human granulocyte colony stimulating factor (G-CSF), produced by recombinant DNA technology. Neupogen® is the Amgen Inc. trademark for Filgrastim, recombinant methionyl human granulocyte colony stimulating factor (r-methHuG-CSF).

7.4.5.3 Drug Availability: Commercially available.

7.4.5.4 Storage: Neupogen® should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, Neupogen® may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.

7.4.5.5 Side Effects: Neupogen® is contraindicated in patients with known hypersensitivity to E. coli-derived products, Filgrastim, or any component of the product. The only consistently observed clinical toxicity described with Neupogen® is medullary bone pain. Other clinical toxicities that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.

7.4.6 G-CSF – Pegfilgrastim (pegylated r-methHuG-CSF, Neulasta®) [10/18/05]

NOTE: Refer to the commercial package labeling for full prescribing information.

7.4.6.1 Dose-Formulation: Neulasta® (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is obtained from the bacterial fermentation of a strain of E. coli bearing a genetically engineered plasmid containing the human G-CSF gene. Neulasta® is available in 0.6 mL pre-filled syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

7.4.6.2 Mechanism of Action: Both filgrastim and pegfilgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function show that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo compared with filgrastim.

7.4.6.3 Drug Availability: Commercially available.

7.4.6.4 Storage: Neulasta® should be stored refrigerated at 2° to 8° C (36° to 46° F); syringes should be kept in their carton and protected from the light until time of use. Shaking should be avoided. Before injection, Neulasta® may be allowed to reach room temperature for a maximum of 48 hours but should be protected from the light. Neulasta® left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta® should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta® should be discarded.

7.4.6.5 Side Effects: Neulasta® is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. Drugs such as lithium may potentiate the release of neutrophils; patients who are taking lithium should have more frequent monitoring of their neutrophil counts. The
The predominant toxicity attributed to Neulasta® in clinical trials was medullary bone pain of mild to moderate severity. Other adverse experiences included nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. Leukocytosis (WBC > 100 x 10^9/L) was observed in less than 1% of subjects. A rare case of hypoxia was also observed. Reversible elevations in LDH, alkaline phosphatase, and uric acid were also observed.

7.5 Adverse Events (8/17/11)
As of October 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, for grading of all adverse events reported via AdEERS. All RTOG case report forms will continue to use CTCAE, v. 3.0.. A copy of the CTCAE v. 4 can be downloaded from the CTEP home page (http://ctep.info.nihcancer.gov) or the RTOG web site, http://www.rtog.org/members/toxicity/main.html. All appropriate treatment areas should have access to a copy of the CTCAE, v. 4..

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

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

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

7.5.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 hours/day)
Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

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

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

7.5.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, available 24 hours/day) within 24 hours of discovery of the event.

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

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

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
Inpatient hospitalization or prolongation of existing hospitalization;
A persistent or significant disability/incapacity;
A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event. Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

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

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

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

7.5.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (8/17/11)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.6 AdEERS Expedited Reporting Requirements (6/22/05)
Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days’ of the Last Dose of the Investigational Agent, thalidomide, in this Study
<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5'</th>
<th>Grades 4 &amp; 5'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected with Hospitalization</td>
<td>Unexpected without Hospitalization</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible Probable Definite</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>24-Hour report within 5 Calendar Days</td>
</tr>
</tbody>
</table>

1. Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
   - AdEERS 24-hour notification followed by complete report within 5 calendar days for:
     - Grade 4 and Grade 5 unexpected events
   - AdEERS 10 calendar day report:
     - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
     - Grade 5 expected events

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

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

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

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

- (8/17/11) Any medical event equivalent to CTCAE, v. 4 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

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

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

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

In Cohort A, an investigational agent supplied under a CTEP-IND is being used in combination with commercial agents. The combination should be considered investigational, and reporting should follow the guidelines described above.

Clinical Trials Agreement

The THALIDOMIDE supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Celgene Corporation (hereinafter referred to as ACollaborator(s)@) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the AIntellectual Property Option to Collaborator@ contained within the terms of award, apply to the use of the Agent(s) in this study:

March 2005
1. Agent(s) may not be used for any purpose 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 shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as “Multi-Party Data.@):
   a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI’s participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator’s wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP 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. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

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

7.8 Chemotherapy Modality Review
Dr. Harmon, the Medical Oncology Co-Chair, will perform two Quality Assurance Reviews for each patient cohort, reviewing data collected prior to surgery and reviewing data collected at the end of postoperative thalidomide. The first review will take place after complete data for the first 10 cases enrolled on each cohort has been received at RTOG Headquarters. The next review will be performed after complete data for subsequent cases enrolled on each cohort has been received at RTOG Headquarters.

8.0 SURGERY
8.1 Initial Biopsy For Diagnosis and Study Tissue
The biopsy ideally should be an open incisional biopsy, as it needs to provide adequate tissue for evaluation and the tumor/stromal interface. The open incision biopsy is preferred, even if the patient had a prior diagnostic thin needle biopsy before being evaluated by the participating RTOG institution. The rationale for the preference is that, in order for the biologic correlates of the study to be analyzed, it is critical to obtain adequate tissue particularly from the tumor/stromal interface. Sufficient tumor must be obtained to determine the histologic subtype of the soft tissue sarcoma and the tumor grade. The biopsy should be done in such a way as to permit excision of the biopsy site at the time of formal resection. If the patient had an initial needle biopsy before being evaluated by the particular RTOG institution, then the needle biopsy site should be tattooed for future identification during and following radiation. If extenuating circumstances would preclude a safe open incisional biopsy (e.g., very deep tumor), multiple core biopsies under CT guidance would be acceptable for entry into the protocol but only with approval from Dr. Eisenberg, Dr. Kraybill, or Dr. Kane.

8.2 Surgery
8.2.1 The surgeon and radiation oncologist will consult after diagnosis and prior to instituting pre-operative therapy. Prior to instituting therapy, the surgeon should also determine and document whether a limb preservation approach versus amputation would be necessary to obtain local control. If possible, every effort should be made to perform limb preservation. If deemed necessary, a plastic surgeon may be consulted.

8.2.2 Resection of the sarcoma will occur following combined pre-operative radiation and thalidomide +/- chemotherapy. The resection should be done with the goal of having negative pathologic margins. Quality assurance for surgical resection will be provided by assessment of the specimen by surgical pathology (see Section 10.3). Microscopic absence of tumor on the inked margins will be accepted as a negative margin resection.

8.2.3 Definitions of operative procedures will be made following pathologic evaluation of the resected specimen. The definitions include:

8.2.3.1 Amputation-margin status will still be assessed and categorized.

8.2.3.2 Limb sparing surgery with the following margin status:

8.2.3.2.1 Intralesional Resection – grossly positive margin – visible tumor left behind. This procedure is not acceptable as a biopsy or a therapeutic resection for the purposes of this protocol. The patient should be assessed for surgical re-excision or will be removed from the protocol.

8.2.3.2.2 Marginal Resection – All gross disease removed; less than compartmental or muscle group excisions; microscopically positive margins. These patients will receive a postoperative radiation boost and will continue on protocol (see Section 6.3).
8.2.3.2.3 **Wide Excision** – Microscopically negative margins, less than compartmental or muscle group excision (for lesion within a specific muscle group), all gross disease removed. Margins are microscopically negative.

8.2.3.2.4 **Radical Excision** – Entire anatomic compartment and negative microscopic margin.

### 8.3 Definitive Surgical Procedure

Surgical treatment necessary to resect the tumor with negative margins should be used. The definitions, as noted above, will be recorded in the surgical form. The goal for all surgery should also be limb preservation, if possible, within the realm of an appropriate oncologic resection.

**8.3.1** The definitive surgical resection for both Cohorts A and B should be performed 42 to 56 days after the last radiation treatment. The rationale for performing surgery prior to or after these time points needs to be clearly documented by the surgeon of record.

### 8.4 Principles of Surgery (7/21/04)

**8.4.1** All lesions of the trunk and extremities will be treated with conservative resection (minimal wide excision) after pre-operative therapy. Any biopsy site should be excised *en bloc* with the definitive surgical specimen. Surgical resection should remove as wide a margin of tissue around the tumor as possible without compromising function. Dissection should always be done through grossly normal tissue planes and should be done beyond the fascial plane adjacent to the tumor. If the tumor is close to or displaces major vessels or nerves, these need not be removed if the adventitia or perineurium is removed and the margin is not involved pathologically. Frozen section at the time of surgery should be performed on the closest margin and should be confirmed as being free of tumor. If post-operative pathologic evaluation reveals positive soft tissue margins other than bone, nerve or large blood vessels, surgical re-resection to obtain negative margins should strongly be considered if it will not have a major impact upon the patient’s functionality. If the margin on bone, major blood vessel or nerve is microscopically positive, additional radiation should be given as noted in the protocol. In general, lymph node dissection is not recommended. Primary tumors overlying major lymph node stations may be better treated with surgical resection to include node dissection. Surgical clips (*titanium*) should be placed to mark the periphery of the surgical field of resection and other relevant structures to help guide the radiation oncologist if post-operative radiation is necessary. Closed suction drainage should be used in all anatomic regions *Hemovac, JP, etc.*. The drains should exit the skin close to the edge of the surgical incision.

**8.4.2** *Clearly* state in the operative note what type of surgical procedure was performed and from where the frozen sections of the margins were taken.

**8.4.3** Because all patients will have had pre-operative radiation, special attention must be given to the skin flaps. Use of muscle flaps, pedicled myocutaneous flaps, and even free flaps is encouraged to fill dead space and provide well-vascularized tissue. These flaps should be used if there is any concern regarding the viability of the skin flaps.

**8.4.4** Because all patients will have pre-operative radiation, if periosteum is resected for an extremity sarcoma, consideration should be given to internal fixation to prevent future fracture.

**8.4.5** In general, the following principles should be followed in post-operative management of these patients:

- **8.4.5.1** Maintain staples or skin sutures per surgeon preference. Due to potential delays in wound healing following preoperative radiation, at least 3-4 weeks is strongly encouraged.

- **8.4.5.2** Leave drains in place until the drainage meets the surgeon’s criteria for removal.

- **8.4.5.3** Begin rehabilitation slowly.

**8.4.6** Resectability will depend upon the judgment of the operating surgeon. As stated in Section 8.3, the goal for all surgery for extremity tumors should be limb preservation, if possible, within the realm of an appropriate oncologic resection. However, some extremity tumors may require amputation to obtain even grossly negative margins. For tumors located in non-extremity anatomic areas, it must be the judgment of the operating surgeon that he/she can reasonably expect to obtain negative margins. Unresectable tumors elsewhere may be
palliated with additional chemotherapy or radiation therapy. Amputation for any reason will be considered a local failure.

8.5 Surgical Toxicity

8.5.1 Wound Complications

All wound complications will be reported using CTCAE 3.0 on the Adverse Event Evaluation Form (AE) or Follow-up Form (F1). Wound Complications can be scored according to one or more of the following CTCAE criteria, according to criteria that best describe the complication: (1) Dermatology/Skin-Wound Complications/non-infectious; (2) Infection: (a) With Grade 3/4 neutrophils, (b) With Grade 1 or 2 neutrophils, (c) With unknown neutrophils, (d) Infection other specify (wound); or (3) Musculoskeletal: (a) Seroma, (b) Soft Tissue Necrosis

8.6 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. The next review will be performed after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy (10/18/05)

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

9.1.1 Anticonvulsants
9.1.2 Antiemetics
9.1.3 Prophylactic anticoagulants – at the discretion of the treating physician anticoagulants may be used to reduce or treat clotting. Recommend 81 mg ASA in the morning during thalidomide if not contraindicated.
9.1.4 Antidiarrheals
9.1.5 Analgesics
9.1.6 Hematopoietic Growth Factors
9.1.6.1 G-CSF: Filgrastim (r-metHuG-CSF, Neupogen®) OR Pegfilgrastim (pegylated r-metHuG-CSF, Neulasta®); see Section 7.1.1.6.
9.1.6.2 EPO/Procrit/Aranesp may be used as indicated along with red cell transfusions.
9.1.7 Colace or Senekot should be given prophylactically for constipation.
9.1.8 Appetite enhancers (i.e., Megace™) [6/17/04]

10.0 TISSUE BANKING/CENTRAL REVIEW/TRANSLATIONAL RESEARCH (6/12/08)

10.1 Tissue Banking (Strongly Recommended)

10.1.1 Rationale

The purpose of the RTOG Biospecimen Resource at the University of California San Francisco is to acquire and maintain high quality specimens from RTOG trials, to provide uniform access of such tissues to investigators for correlative studies, and to preserve tissue from each block through careful block storage and processing for future studies. Correlative studies using these specimens are meant to integrate new research findings into future protocol development and to provide tissue for future correlative grant applications, testing important biologic questions.

10.1.2 Specimen Collection

Tissue specimens for banking should be taken from both pre-study diagnostic biopsy and from surgical specimen. The biopsy specimen should ideally be an open incisional biopsy (see Section 8.1) to ensure adequate tissue for translational research studies (see Section 10.4). Specimens for tissue banking will be stored for an indefinite period of time (see Section 10.5).
10.2 RTOG Biospecimen Resource (6/22/05)

10.2.1 The following must be submitted to RTOG Biospecimen Resource for the purpose of a) tissue banking for future studies; b) central pathology review (see Section 10.3) and; c) translational research (see Section 10.4):

10.2.1.1 All H&E stained slides processed from the pre-treatment biopsy specimen (can be recut) for central review.

10.2.1.3 All H&E stained slides processed from the post-treatment surgical specimen (can be recut) for central review.

10.2.1.4 A paraffin-embedded tissue block of the tumor from both the pre-treatment biopsy specimen and the post-treatment surgical specimen (A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue), punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the RTOG Biospecimen Resource.)

10.2.1.5 If paraffin block is not available for either pre-operative or post-operative specimen, may substitute 20 unstained slides for each.

10.2.1.6 Block and/or slides (or core if applicable) must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.1.7 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.1.8 A Specimen Transmittal Form; the form must include the RTOG protocol number and patient’s case number.

10.2.1.9 (6/12/08) Submit materials as follows:

Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, DHL, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.2.1.10 Reimbursement (6/12/08)
RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue; $200 per case for a block or core of material; $100 per case for 10-12 slides, $50 per case for urine, $300 per case for complex material (blood, serum, buffy coat cells).
After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.3 Central Review (Mandatory)
After the study has met its accrual, central review will be performed retrospectively by Dr. David R. Lucas for every case.

10.3.1 Pathology Parameters to be Assessed by Central Review
The following parameters will be assessed both for the biopsy and post-treatment resection specimens:
10.3.1.1 Histopathologic Assessment of Biopsy Specimen
a) Sarcoma phenotype as categorized by the WHO (2002)[1]
b) Histologic grade. All tumors in this study will be graded by Central Pathology Review using the French Federation of Cancer Center System [2].
c) Mitotic rate (___ per 10 high power fields)
d) Necrosis (0, < 50%, or > 50%)
e) Tumor matrix (spare, myxoid, fibromyxoid, or fibrous)
f) Vascular space invasion (+/-)
g) Substantial host lymphoplasmacytic response (+/-)
h) Margin of infiltration (pushing, infiltrative, not evaluable)

10.3.1.2 Assessment of Resected Tumor
10.3.1.2.1 Handling of Gross Specimen and Elements to be Included in the Surgical Pathology Report
a) External surface of specimen should be painted with India ink prior to sectioning.
b) Tumor should be bread-loafed at 1 cm intervals with careful attention to margins.
c) Closest gross margin (in cm) must be reported.
d) Gross description of the relative percentages of fleshy, fibrous, gelatinous, necrotic, and hemorrhagic areas, and presence and size of cystic cavities should be included in the pathology report.
e) Tumor should be thoroughly sampled (at least 1 section per 1 cm of greatest tumor dimension).

10.3.1.2.2 Gross Parameters of Tumor
a) Tumor size (___ cm greatest dimension)
b) Description of surgical margin (intralesional, marginal, or wide)

10.3.1.2.3 Histopathological Assessment
a) Percent of viable neoplasm (*0%, < 25%, 25-50%, >50-75%, > 75%)
   * (0% also includes tumors with only rare, degenerated, nonviable-appearing tumor cells)
b) Percent of coagulative tumor cell necrosis (0, < 50%, > 50%)
c) Degree of fibrosis/hyalinization (0, < 50%, > 50%)
d) Tumor margin (pushing, infiltrative)
e) Substantial host lymphoplasmacytic response (+/-)
f) Vascular space invasion (+/-)
g) Closest surgical resection margin (___ cm)
h) Degree of intra tumoral hemorrhage (0, < 50%, > 50%)

10.4 Translational Research (Strongly Recommended)
10.4.1 Rationale: The RTOG has been collecting pretreatment diagnostic tissue from all of the soft tissue sarcoma protocols over the last eight years. A number of histologic, cell kinetic/proliferation, angiogenesis, and molecular markers have been and are under investigation. A number of biomarkers are under investigation by the RTOG Sarcoma TRP group. The results of these ongoing studies will lead to the investigation of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified in future trials, and 2) developing novel treatment strategies which target the molecular abnormalities identified. The goal is to measure ten biomarkers using the archived pathologic material. In this study a number of immunohistochemical studies will be performed on the biopsy specimens to evaluate prognostic and therapeutic targets in the tumors.

10.4.2 Planned Tissue Studies on Paraffin Blocks or Unstained Slides
10.4.2.1 Specimen Collection: Tissue from the incisional biopsy and surgical specimens should be fixed in buffered formalin for no more than 24 hours and embedded in paraffin for optimum results. In the absence of paraffin block, 20 unstained slides may be substituted. See Sections 10.2.1.4 and 10.2.1.5.

10.4.2.2 Microvessel density and assessment of tumor angiogenesis
Angiogenesis is the process of tumor-induced new blood vessel formation, which enables the creation of a host-derived vascular network feeding the growing malignant
A substantial body of literature clearly supports the notion that angiogenesis is a critical pathway in tumorigenesis. Without it, solid tumors cannot progress much beyond 1-3 mm in size, nor can they metastasize hematogenously.

The degree of tumor angiogenesis is reflected in the assessment of microvessel density (MVD) within tumor specimens. High MVD is associated with a worse prognosis in a multitude of solid tumors including cancers of the brain, breast, bladder, kidney and prostate.

The biologic impact of MVD in sarcoma remains under study. A host of studies show a correlation between high MVD and poor prognosis in sarcomas. In contrast, some studies did not show a correlation between STS MVD and clinical outcome. Given that thalidomide possesses anti-angiogenesis activity, assessment of tumor MVD in this study will provide important new information about angiogenesis as a prognostic factor and target in soft tissue sarcomas.

Biological/Prognostic Markers

uPA / tPA / PAI-1 Assessment: Urokinase-like plasminogen activator, and tissue-like plasminogen activator (uPA, tPA) are proteases that can activate other proteases, digest extracellular matrix and promote cancer invasion and metastasis. In addition, this pathway is active in tumor angiogenesis, and increased endothelial expression results in enhanced blood vessel formation. Plasminogen Activator Inhibitor –1 (PAI-1) is the prototypical uPA/tPA inhibitor. It binds to its target with high affinity and permanently destroys its function. In addition, PAI-1 attaches to vitronectin and inhibits integrin (αvβ3, αvβ5) mediated cell attachment and migration. The microenvironment interplay between PAI-1 and uPA, tPA, determines both tumor invasiveness and angiogenesis. Indeed, clinical studies show that high sarcoma uPA levels correlate with increasing tumor grade and metastatic risk. Thus, histologic assessment of the uPA / tPA / PAI-1 pathway will provide new insight into its role in sarcoma biology, and its importance as a molecular target for therapy.

EGFR, p53, Ki-67, TUNEL

The relative balance between cell growth and cell death determines the net therapeutic response. Ki-67 is a marker for cell proliferation, whereas TUNEL is an indicator of apoptotic cell death. Epidermal Growth Factor Receptor (EGFR) overexpression and activation by ligand correlate with radioresistance. Preclinical studies have demonstrated enhanced radiation- and chemotherapy-induced tumor cytotoxicity when EGFR antagonists are implemented. In addition, there is cross-talk between the EGFR and angiogenesis pathways. Accordingly, the ability of EGFR as a marker to discriminate for potential treatment response is currently a topic of intense interest. These studies will provide insight into tumor biology and response to treatment.

Biologic studies will be performed on paraffin sections of the pretreatment biopsy and the post-treatment surgical specimens:

- Microvessel Density: assessed with antibodies to CD31 and factor VIII-related antigen
- Biological/prognostic markers: assessed with antibodies to EGFR, p53, Ki-67
- Apoptosis: assessed by means of the terminal-dioxynucleotidyltransferase-mediated dUTP nick-end labeling (TUNEL) assay. Additional markers (Tissue Factor, TPA, UPA, and PAI-1)

Analysis of tissue sections

At least ten random fields over 2 noncontiguous tumor sections with less than 20% necrosis will be assessed. At RPCI, computer-assisted color digital video microscopy and image analysis will be carried out at on a fully motorized Leica DMRA2 microscope with motorized stage and an Hamamatsu C5810 3-chip CCD RGB camera connected to a Pentium IV Windows NT workstation for image analysis. Computer algorithms for digital image analysis are used to segment positively stained nuclei or cytoplasmic areas from images of histologic sections. The observer defines the parameters of analysis (i.e.: positive vs. negative, vs. background) and then teaches the software to recognize this.
Biological features are quantitated and analyzed on a cell by cell basis. Once the performance of the algorithm is optimized, image analysis is executed in an automated batch job mode. The value and distribution of all the measured parameters (cell shape, staining intensity etc.) within the tumor section will be assessed and documented. From this, the absolute and relative number of positive cells as well as their distribution and heterogeneity will be derived.

10.4.3 Planned Studies on Circulating Factors Utilizing Whole Blood

10.4.3.1 Specimen Collection:
8 cc of blood needs to be collected at various treatment time points (5) for analysis that will evaluate circulating angiogenic growth factors (VEGF, and bFGF) as well as circulating endothelial cells (CEC). The following collecting time points should be noted on the Reporting Form For Circulating Factor (Appendix IV) accompanying the blood samples:

Cohort A sample:
   a. pre-treatment (baseline)
   b. at the end of the second course of radiation/thalidomide before starting 3rd cycle of MAID
   c. on the day starting the post-op adjuvant thalidomide
   d. at the 3-month time point post-op after starting adjuvant thalidomide
   e. at the 3-month follow-up time point after completion of post-op thalidomide

Cohort B sample:
   a. pre-treatment (baseline)
   b. during week four of the pre-op RT/thalidomide
   c. on the day starting the post-op adjuvant thalidomide
   d. at the 3-month time point after starting post-op adjuvant thalidomide
   e. at the 3-month follow-up time point after completion of post-op adjuvant thalidomide

10.4.3.2 Sample Acquisition and Storage:
Patients entered into the study in either Cohort A or B will have one tube of blood (8 cc) submitted at each specified time point indicated above for a total of 5 during patient treatment and follow-up. The blood will be collected in yellow top ACD tubes and shipped at room temperature within 24 hours of blood collection to:

James C. Watson, MD
Fox Chase Cancer Center
7701 Burholme Avenue, Room C403
Philadelphia, PA 19111
(215-214-1437)

Include patient’s RTOG identification number, date of collection, as well as type of specimen (a-e) see Section 10.4.3.1. Please ship via overnight and do not ship on Friday, Saturday or Sunday.

10.4.3.3 Reimbursement for Whole Blood Submitted to Fox Chase: (6/12/08)
RTOG will reimburse institutions $300 per serum submission, To be reimbursed, sites must submit an invoice including institution number and address, study, and case number to:

American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: Clinical Trials Administration

10.4.3.4 Analysis of Circulating Angiogenic Growth Factors (Purpose):
   • To assess changes in soluble circulating angiogenic growth factor levels of VEGF and bFGF from baseline correlated to levels during RT/thalidomide, surgical resection, post-op adjuvant thalidomide, and baseline post-op off all therapy.
• To correlate changes to both single patient data and pooled patient data variables.
• To correlate changes to the number and characterization of CEC.
• To correlate changes to tumor and tissue factors for both individual and pooled patient database. The factors include tumor grade, apoptosis, tissue MVD, and the angiogenic related biomarkers (see Section 10.2).

10.4.3.5 Laboratory Methods:
Enzyme-linked immunosorbent assay (ELISA) will be used to determine plasma VEGF and bFGF levels using a quantitative sandwich enzyme immunoassay technique (Quantikine® Human VEGF and bFGF Immunoassay, R&D Systems, Minneapolis, MN). Solid phase monoclonal and an enzyme-linked polyclonal antibody raised against recombinant human VEGF and bFGF will be used. Optical densities are determined using a microtiter plate reader at 450 nm for VEGF and 490 nm for bFGF. The calibrations on each microtiter plate will utilize recombinant human VEGF standards, created by plotting the logarithm of the mean absorbance of each standard versus the logarithm of the VEGF concentration. The growth factor distributions are expected to be nonnormal, and, therefore, nonparametric testing is likely to be used. Wilcoxon’s signed rank-test will be used for paired comparisons of growth factor concentrations obtained at different time points. The Kruskal-Wallis/Mann-Whitney tests will be used for correlating growth factor levels with tumor status and immunohistochemical analysis.

10.4.3.6 Circulating Endothelial Cells: (CEC)
Angiogenesis is the formation of new blood vessels. It is required for various physiologic and pathologic processes including wound healing, menstrual cycling, and tumor growth and metastasis. It also requires the recruitment of endothelial cells to the sites of injury or the tumor bed. These endothelial cells may be derived from two different sources – (1) migration of mature endothelium from preexisting vessels or (2) recruitment of endothelial progenitor cells from the circulation. In recent years, there has been increasing evidence that the human circulation contains both mature and immature endothelial cells.

The first description of circulating endothelial cells (CEC) was in 1964 in leukocyte concentrations of patients with tumors. Several laboratories have demonstrated the presence of CEC in normal and pathologic conditions, such as sickle cell crisis, myocardial ischemia, septic shock, and cancer. The initial descriptions of CEC were of mature endothelial cells, which were most likely shed from the walls of existing blood vessels secondary to trauma or intravascular turbulence. However, other investigators have now demonstrated that CEC may originate in the bone marrow as circulating endothelial progenitor cells (EPC) expressing markers such as vascular endothelial growth factor receptor 2 (VEGFR-2 or KDR), CD133, and CD34. These can contribute to the formation of new blood vessels or replacement of endothelial cells lost from existing ones.

Therefore, the requirement for neoangiogenesis may be fulfilled by two different endothelial cell sources. Some endothelial cells (measured by CEC) come from existing blood vessels. However, this cannot account for all neoangiogenesis. Endothelial cells must also be recruited from the circulation, and this may represent endothelial progenitor cells summoned from the bone marrow.

This biological correlative study will investigate CEC as a potential angiogenesis surrogate. CEC number is modulated by normal physiologic processes such as menstruation and a variety of disease states including malignancy. Furthermore, pharmacologic alteration of CEC phenotype has been demonstrated. This preliminary work has provided a compelling rationale for proceeding with CEC enumeration in cancer patients treated with antiangiogenic therapies in an attempt to demonstrate treatment effect. Both flow cytometry (FC) and immunohistochemistry will be used as a methodology for CEC enumeration and delineation.
10.4.3.7 **Methods:**

CEC will be quantified from peripheral blood of study patients at designated time points using immunohistochemistry (IHC) and flow cytometry (FC). Peripheral blood mononuclear cells (PBMCs) will be isolated using Ficoll separation. For IHC, cytopsins made of PBMC will then be stained with an endothelial cell specific antibody (CD146 or P1H12). Early passage HUVEC will be stained in parallel as a positive control. Intact P1H12/CD146-labelled nucleated cells present that stain above background will be enumerated. At least three cytopsin slides, each corresponding to .333 ml whole blood, will be assessed at each time point by a single observer in order to calculate the concentration of CEC/ml whole blood (3x average # CEC/cytopsin slide). For FC, 4-color FACS analysis will be performed using a panel of monoclonal antibodies including CD45, P1H12, VEGFR-2 (KDR), CD34, and CD133. CEC will be quantified as the number of P1H12+ cells/100,000 PBMC. This panel of antibodies will be used to determine endothelial cell lineage and characterize maturity (distinguish precursor from more mature cells).

10.4.3.8 **Preliminary Data:**

Our initial results in the laboratory investigation of CEC involved defining endothelial lineage by a 4-color flow cytometry of peripheral blood mononuclear cells (PBMC) utilizing a panel of monoclonal antibodies. These were CD45, CD34, CD146, KDR, and CD133. An endothelial progenitor cell can be described as expressing some combination of CD133, KDR, and/or CD34. Similarly any PBMC, which expresses CD 146 and not CD45 or CD133, can be defined as a mature endothelial cell. Further CD146 cells that are also KDR positive are defined as intermediate CEC, while sloughed mature endothelial cells are defined as CD146 positive cells, which are CD45 and KDR negative. We further established baseline variability in normal controls by IHC and determined that CEC number for males vs. females do not differ significantly. There was, however, a difference in number of CEC in young vs. older women with young menstruating females having a significant increase in comparative number of CEC. There was no difference noted in number of CEC in older men vs. older women. These similarities in CEC number were not affected by diurnal variation. When comparing cancer patients to non-cancer patients although there was no overall difference in CEC values, multicolor FACS analysis revealed a significantly greater number of mature CEC in cancer patients vs. non-cancer patients. In addition there was 6-fold increase (significant) in the number of endothelial progenitor cells in cancer patients vs. non-cancer patients. These preliminary data from our lab provide a basis for analysis of CEC numbers and lineage by reproducible methods to be utilized in clinical trials employing antiangiogenic agents. Investigations of this type have also been highlighted recently by preliminary observations from other investigators. Several investigations have demonstrated that CEC are elevated in cancer patients and that these numbers can be modulated with antiangiogenic agents. However these reports have not characterized CEC lineage in cancer patients or changes in this expression pattern during therapy. Utilizing 4-color flow FACS and the ability to define lineage specific cell population of CEC will enhance this pilot proposal and provide data for further evaluation in planned future trials.

10.5 **Confidentiality/Storage (6/12/08)**


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

10.5.2 Specimens for central review will be retained until the study is terminated and the review is completed; specimens for IHC and marker studies and tissue banking will be stored for an
indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

### 11.0 PATIENT ASSESSMENTS

#### 11.1 Study Parameters (6/22/05)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study Entry</th>
<th>Prior to Each MAID Cycle</th>
<th>Every Week During MAID</th>
<th>During XRT and THAL</th>
<th>Prior to Surgery</th>
<th>Follow-up every 3 months in years 1-2</th>
<th>Follow-up every 6 months in years 3-6</th>
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<td>MRI or CT of primary, with contrast</td>
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<td>X</td>
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<td>Chest CT</td>
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<td>Biopsy (ideally incisional)</td>
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<td>CBC (including ANC), electrolytes, BUN, glucose, AST &amp; ALT, creatinine, PT/PTT, fibrin split, fibrinogen</td>
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<td>X</td>
<td>X₉</td>
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<td>X₉</td>
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<td>Chest X-ray</td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood for circulating factors</td>
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<td>X₈</td>
<td>X₉</td>
<td>X₈</td>
<td>X₉</td>
<td>X₉</td>
<td>X₉</td>
</tr>
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</table>

a. Must be done prior to biopsy;
b. Must be done within 10 weeks prior to registration;
c. Must be done within 8 weeks prior to registration;
d. Must be done within 2 weeks prior to registration;
e. Must be done within 48 hours prior to registration and within 24 hours of thalidomide administration (see Section 3.1.7); then every week during the first 4 weeks of treatment, every 4 weeks while on thalidomide if periods are regular or every 2 weeks if periods are not regular, and at 4 weeks after the last dose of thalidomide (see Section 3.1.6.4);
f. MUGA or Echo required for Cohort A patients; EKG is recommended, not required;
g. Strongly recommended; a total of 5 blood samples to be collected (see Section 10.4.3.1 for details);
h. For Cohort B, only CBC once a month is necessary;
i. CT or MRI of the primary site is done every 6 months for the first 2 years, then annually thereafter until year 5;
j. Physical exams should be done weekly.

### 11.2 Response Assessment

#### 11.2.1 Measurement of Response

Response will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-
measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy. Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm with conventional techniques (CT, MRI, x-ray) or as > 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Target Lesions: All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

11.2.1.1 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Response to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination. In addition, pathologic response will be recorded at the time of pathologic review of the resected specimen (see pathology section).

11.2.2 Response Criteria

Response and progression to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination. In addition, pathologic response will be recorded at the time of pathologic review of the resected specimen (see pathology section).

11.2.2.1 Evaluation of target lesions

- **Complete Response (CR):** Disappearance of all target lesions as measured by MRI, CT, or physical examination. This is the order of preference for measurement.
- **Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter (LD) of target lesions. The order of preference for measurement is MRI, CT, or physical examination.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. The order of preference for measurement is MRI, CT, or physical examination.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
11.2.2 Disease Progression
If progressive disease is noted after any pre-operative cycle, the patient will be offered surgical therapy immediately. Patients who develop systemic metastatic disease will be considered treatment failures and will be removed from protocol treatment, but follow-up data will still be collected. They may be treated with other forms of palliative chemotherapy.

11.3 Wound Complications
Wound Complications can be scored according to one or more of the following CTCAE, v. 3.0 criteria, according to criteria that best describe the complication: (1) Dermatology/Skin-Wound Complications/non-infectious; (2) Infection (Wound): (a) With Grade 3/4 neutrophils; (b) With Grade 1/2 neutrophils; (c) With unknown neutrophils, or (3) Musculoskeletal: (a) Seroma (b) Soft Tissue Necrosis

12.0 DATA COLLECTION (7/21/04)
Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

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

12.1 Summary of Data Submission (5/18/06)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
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</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
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<tr>
<td>Initial Evaluation Form (I1)</td>
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<tr>
<td>Pathology Report (P1)</td>
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<tr>
<td>Slides/Blocks (P2)</td>
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<tr>
<td>Dosimetry Information</td>
<td>Within 1 week of end of RT</td>
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<td>Dose Calculation Form (TL)</td>
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<tr>
<td>Films (Simulation and Portal or DRRs of All Fields) (TP)</td>
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<tr>
<td>Complete Daily Treatment Record (T5)</td>
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<td>Composite Isodose Distribution (T6)</td>
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<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 Week of end of pre-op RT and within 1 week of end of boost RT, if applicable</td>
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<tr>
<td>MAID Treatment Form (TF)</td>
<td>After each cycle of MAID</td>
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<tr>
<td>THAL Treatment Form (SF)</td>
<td>After each cycle of thalidomide and post-op every 3 months</td>
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<tr>
<td>Surgical Form (S1)</td>
<td>Within 4 weeks of surgery</td>
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<td>Surgical Operative Report (S2)</td>
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<td>Surgical Path Report (S5)</td>
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<tr>
<td>Follow-up Form (F1)</td>
<td>At the time of pre-surgical eval, q 3 months (from the initially submitted F1) x 2 years; q 6 months x 4 years. Also at progression/relapse and at death</td>
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</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
13.1.1.1 Treatment delivery (as defined in Section 13.2)

13.1.2 Secondary Endpoints
13.1.2.1 Toxicity (rates of Grade 3, 4, and 5 as measured by the CTCAE version 3.0)
13.1.2.2 Wound Complications (rates of grade 2, 3, 4, and 5 using CTCAE version 3.0)
13.1.2.3 Biological Correlates of Anti-Angiogenic Effect
13.1.2.4 Response to pre-operative therapy
13.1.2.5 Local Failure (Failure: persistent or recurrent local disease or amputation)
13.1.2.6 Disease-Free Survival (Failure: persistent or recurrent local disease or amputation, distant metastases, new primary, or death)
13.1.2.7 Distant Disease-Free Survival (Failure: distant metastases or death)
13.1.2.8 Overall Survival (Failure: death due to any cause)

13.2 Overview and Sample Size

There is no prior experience with the treatment regimen in either cohort. RTOG 0330 is designed as a pilot study following discussion with the NCI drug branch to generate baseline information about toxicity, treatment delivery, and laboratory correlative studies, which can be used later to design a more definitive phase II or III trial. The sample size of patients per cohort was arbitrarily set at 20 patients during that discussion. Patients will be enrolled in a non-randomized manner into 2 cohorts:

Cohort A will consist of patients with high/intermediate-grade disease.
Cohort B will consist of patients with low-grade disease.

Patients in Cohort A will be treated with pre-operative RT and thalidomide, with the addition of 3 cycles of MAID, followed by surgery and twelve months of thalidomide. Patients in Cohort B will be treated with pre-operative RT and thalidomide, followed by surgery and 6 months of adjuvant thalidomide. All of the endpoints will be reported separately for each cohort.

The primary endpoint is treatment delivery. In RTOG 95-14, 89% of patients received the protocol dose of RT within 5%, and 79% received all 3 pre-operative cycles of MAID. For this study, a patient will be considered compliant if they receive at least 95% of the pre-operative protocol dose of RT, all 3 cycles of MAID (if applicable), and receive thalidomide on 75% of the days during radiation as prescribed per protocol. If the compliance rate is at least 75% (for an individual cohort), then that cohort will be considered for further study. For planning purposes, we assume a 10% noncompliance rate and will accept a noncompliance rate of 25%. If 6 or more patients are classified noncompliant for a particular cohort, the associated treatment will not be considered for further study. The plan has a Type I error of 0.011 and Type II error of 0.41 (i.e., 0.59 statistical power).

In RTOG 95-14, 78% of the 59 patients experienced a grade 4 hematologic toxicity with 3% dying from toxicity. Twenty percent of them experienced grade 4 non-hematologic toxicities. In this study, we do not expect any further increase in rate of grade 4 hematologic toxicity on Cohort A (MAID). We will monitor the incidence of possible treatment related deaths. If there is any fatal treatment morbidity, the case will be immediately reviewed by the principal study chair, followed by a conference call with other study chairs to determine if a dose modification is warranted. If there are two such fatal treatment morbidities, accrual will be immediately suspended pending review by the study chairs. If confirmed, termination of further new patient accrual may be considered at this point. An increase in the grade 4 non-hematologic toxicity rate to 35% would be considered unacceptable.
The RTOG has not conducted a previous study in low-grade patients (Cohort B). 10-15% grade 4 non-hematologic toxicities would be a projected rate with RT alone in this patient group. A rate of 25% or higher would be considered unacceptable.

13.3 Patient Accrual

RTOG 95-14 accrued approximately 1.9 patients per month. Based on these results, the expected monthly accrual is 2 patients per month for the high/intermediate grade (Cohort A) group. In addition, we project an additional accrual of 2 patients per month for the low-grade (Cohort B) group. Allowing for approximately 6 months at the beginning of the study for institutional IRB approvals, patient accrual to both cohorts should be completed in 17 months. As soon a cohort reaches target accrual, it will be closed to patient accrual but the study will continue to enroll patients into the other cohort.

13.4 Analysis and Reporting Plan

13.4.1 Statistical Methods

13.4.1.1 Clinical Endpoints

The rates of successful treatment delivery, serious toxicity, and wound complications will be estimated using a binomial distribution. The local failure rate will be estimated using the cumulative incidence method as this accounts for the competing risk of death without local failure. Overall, disease-free, and distant disease-free survival will be estimated using the Kaplan-Meier method. All rates will be accompanied by their associated 95% confidence intervals. All study endpoints will be analyzed separately for each cohort.

13.4.1.2 Biological Endpoints

Whole blood will be collected for bFGF, VEGF, and circulating endothelial cells at the following time points: 1) pre-treatment (baseline), 2) during pre-operative RT/Thalidomide, 3) after surgery, 4) during adjuvant Thalidomide, and 5) at discontinuation of adjuvant Thalidomide. The percentage change will be calculated from baseline to each of the other time points within and across patients. An exploratory analysis of these data in each patient cohort will be performed that may generate hypotheses and establish cut points for future testing.

13.4.2 Interim Reports

This study will be monitored by the Clinical Data Update System (CDUS), version 3.0r2. Full reporting of cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Interim reports are prepared every six months for publication in the RTOG meeting book until the primary endpoint is analyzed. In general, these reports will include: patient accrual rate and projected completion date; institutional accrual; distribution of pretreatment patient characteristics; compliance rate of treatment delivery with respect to the protocol prescription; the frequency and severity of toxicity.

13.4.3 Analysis and Reporting of Initial Treatment Results

13.4.3.1 Primary Endpoints

The analysis to report the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are: patient accrual rate; institutional accrual; patients excluded with their reasons for exclusion; distribution of pretreatment patient characteristics; observed results with respect to the endpoints described in Section 13.1. The focus of this report will be on endpoints 13.1.1.1 and 13.1.2.1-13.1.2.3 (treatment delivery, toxicity, wound complications, biological correlates).

13.4.3.2 Secondary Endpoints

A second report of the study will be undertaken when each patient has been potentially followed for a minimum of 24 months. The focus of this report will be on endpoints 13.1.2.4-13.1.2.8 (local failure, disease-free survival, distant disease-free survival, overall survival).

13.5 Inclusion of Women and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we have also considered
the possible interaction between race and treatment. Based on the accrual statistics from RTOG 95-14, we project that 80% of patients enrolled to this study will be white, and 20% black. The rates described in Sections 13.1 and 13.2 can be estimated with standard error ≤ 0.125 for whites, and ≤ 0.250 for blacks. The following table lists the projected number of patients in each gender, race, and ethnic category.

**Planned Gender and Minority Accrual Estimates**

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<td></td>
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<td>Males</td>
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REFERENCES


A PILOT PHASE II STUDY OF PRE-OPERATIVE RADIATION THERAPY AND THALIDOMIDE (IND 48832; NSC 66847) FOR LOW GRADE PRIMARY SOFT TISSUE SARCOMA OR PRE-OPERATIVE MAID/THALIDOMIDE/RADIATION THERAPY FOR HIGH/INTERMEDIATE GRADE PRIMARY SOFT TISSUE SARCOMA OF THE EXTREMITY OR BODY WALL

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 soft tissue sarcoma.

WHY IS THIS STUDY BEING DONE?

This research is being done because better treatments for controlling soft tissue sarcomas are needed. The standard treatment for patients with large soft tissue sarcomas is generally radiation therapy, surgery, and sometimes chemotherapy to try to prevent the cancer from returning.

The purpose of this study is to find out what effects (good and bad) the addition of the drug, thalidomide (an experimental treatment), to chemotherapy and/or radiation, and surgery might have on you and your cancer and whether this experimental treatment with thalidomide is more effective than the previous RTOG study for sarcoma treatment.

Thalidomide is a drug that has been used in cancer patients to prevent the growth of new blood vessels in tumors with the hope that this will help control and perhaps prevent the cancer from coming back. In addition, testing will be done on blood and tumor tissue to find out if this combination of treatment can have a measurable effect on tumor blood vessel growth.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 44 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Patients will be divided into two groups depending on the type of their sarcoma.

**Group A**

Patients will receive three cycles of combination chemotherapy through a vein every three weeks, alternating with two courses (11 treatments) of radiation therapy (RT) given with thalidomide. The chemotherapy will consist of a combination of the drugs mesna, adriamycin, ifosfamide, and dacarbazine (MAID). Each cycle of chemotherapy (MAID) is given over 4 days. Patients may stay in the hospital for each cycle if their doctor feels it is necessary. The RT will be given once a day, Monday through Friday, over 15 days, and thalidomide will be taken during RT.

The day after each cycle of chemotherapy ends, a drug, G-CSF, will be given by injection. This drug may decrease the chance of infection, which is a possible result of the low blood counts caused by the chemotherapy drugs (MAID). G-CSF will be continued daily until blood counts improve.
Following the third cycle of chemotherapy, the tumor will be removed surgically. If there are any tumor cells at the edges of the removed tissue, an additional 8 treatments of RT will be given with thalidomide, once a day, Monday through Friday. Then patients will receive thalidomide for 12 months.

<table>
<thead>
<tr>
<th>MAID</th>
<th>RT and Thalidomide</th>
<th>MAID</th>
<th>RT and Thalidomide</th>
<th>MAID</th>
<th>Surgery</th>
<th>RT and thalidomide if tumor cells at the edges of removed tissue</th>
<th>Thalidomide for 12 months</th>
</tr>
</thead>
</table>

**Group B**
Patients will receive radiation therapy (RT) once a day, Monday through Friday, for 25 treatments over 5 weeks at the same time as they are receiving thalidomide. After RT, patients will continue to take thalidomide until one week prior to surgery. The tumor will be removed surgically 42-56 days after RT. If there are any tumor cells at the edges of the removed tissue, an additional 8 treatments of RT will be given with thalidomide, once a day, Monday through Friday. Then patients will receive thalidomide for 6 months.

<table>
<thead>
<tr>
<th>RT and Thalidomide</th>
<th>Continue Thalidomide until 1 week prior to surgery</th>
<th>Surgery</th>
<th>Post-op RT and Thalidomide if tumor cells at the edges of removed tissue</th>
<th>Thalidomide for 6 months</th>
</tr>
</thead>
</table>

**Both Groups**
Radiation is given as an outpatient. The radiation treatments take a few minutes and are given once a day, Monday through Friday. All patients will receive thalidomide during their radiation treatments. Thalidomide is a capsule taken by mouth. All patients will be given thalidomide after surgery for either 12 months (Group A) or 6 months (Group B), in an attempt to keep the tumor from coming back. While on thalidomide, patients will take a baby aspirin once a day unless told not to by their doctor.

You will have the following tests and procedures to determine if you can be put on the study. Depending on when you may have had these tests done before, you may or may not need to have them repeated.

Procedures that are Part of Regular Cancer Care: *(6/22/05)*
Before treatment:
- Contrast-enhanced MRI or contrast CT of tumor and extremity before biopsy (removal and examination of a small part of tissue)
- Biopsy
- Chest CT scan
- Blood and urine tests
- Heart function study (Group A)
- EKG, if recommended by your doctor
- All females of childbearing potential must have a urine pregnancy test

If you take part in this study, you will have the following tests and procedures in addition to those above:
Procedures Being Done or Being Done More Frequently Because of the Study:

• Frequent physical examinations by your doctor during your treatment
• Blood tests to check your blood counts, liver function, and kidney function during treatment and/or prior to surgery
• MRI or CT scans to measure the size of your tumor before beginning treatment (as above) and prior to surgery
• MRI or CT scans every 6 months following treatment for the first 2 years then once a year
• All female patients of childbearing potential must have a urine pregnancy test within 24 hours prior to thalidomide administration, every week during the first 4 weeks of therapy; then every 4 weeks while on thalidomide if menstrual periods are regular or every 2 weeks if not regular; and at the last follow-up visit.
• Some of the tissue that is left over from your biopsies and surgery will be sent to a central office for review and research

HOW LONG WILL I BE IN THE STUDY?

Patients in Group A will receive treatment before surgery for a period of 4 months. If there are any tumor cells at the edges of the tissue removed, an additional 8 treatments of RT will be given with thalidomide, once a day, Monday through Friday. Patients will take thalidomide for 12 months after surgery.

Patients in Group B will receive treatment before surgery for a period of 3 months. If there are any tumor cells at the edges of the tissue removed, an additional 8 treatments of RT will be given with thalidomide, once a day, Monday through Friday. Patients will take thalidomide for 6 months after surgery.

All patients will be seen in follow-up visits at least every 3 months for 2 years, although it may be more frequent if necessary. Then follow-up visits will take place every 6 months during the 3rd through 6th years.

The investigator and/or your doctor may decide to take you off the study if it is in your best interest medically, drug supply is insufficient, or new information becomes available. If your disease begins to grow despite the treatment, then the treatment will be stopped. Your doctor will discuss alternative plans for continued care with you at that time. If you stop treatment on this study, your doctor will continue to collect general information about your health status, and any other treatments you may receive, every 3 months.

You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits. If you decide to stop participating in the study, we encourage you to discuss your decision with your doctor.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects described below. You should discuss these with your doctor and/or with a member of the research study team. There may also be other side effects that we cannot predict. You may receive other drugs to make side effects less serious and make you more comfortable. Many side effects go away shortly after treatment is stopped, but in some cases side effects can be serious or long lasting, or even permanent.
Chemotherapy (MAID)
Some patients may be unable to tolerate this chemotherapy due to serious side effects and/or pain.

Very Likely
- Loss of hair, temporary
- Nausea and/or vomiting
- Loss of appetite
- Decreased blood counts that may increase the chance of infection or bleeding

Mesna
Very Likely
- Diarrhea
- Nausea and/or vomiting
- Abdominal pain
- Headache
- Tiredness
- Rash
- Joint and muscle pain

Less Likely, but Serious
- Low blood pressure
- Allergic reactions

Doxorubicin (Adriamycin)
Very Likely
- Nausea and/or vomiting
- Mouth sores
- Diarrhea
- Hair loss, temporary
- Discoloration of nails, skin, and urine
- Fever
- Rapid heart beat
- Decreased blood counts, which could lead to an increased risk of infection, weakness, or bleeding complications. You might need antibiotics, hospitalization, and/or transfusions if these problems are severe.
- If some of the drug accidentally leaks out of the vein where it is injected, severe irritation and ulceration (open sore) of the skin and soft tissues can occur.

Rare
- Sudden death

With prolonged usage of doxorubicin, there is a risk of heart damage, which might be permanent. Symptoms of heart damage include shortness of breath, decreased exercise tolerance, and swollen ankles.

Ifosfamide
Very Likely
- Nausea and/or vomiting
- Loss of appetite
- Mouth sores
- Constipation and/or diarrhea
- Hair loss, temporary
- Rash and/or itching
• Blood in the urine
• Drowsiness
• Dizziness
• Confusion
• Vein inflammation
• Abnormalities of liver and kidney blood tests, which usually do not lead to significant health problems.
• Decreased blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. You might need antibiotics, hospitalization, and/or transfusions if these problems are severe.
• Low or high blood pressure

Dacarbazine

**Very Likely**
• “Flu-like” symptoms of fever, severe nausea and vomiting, chills, and tiredness
• If some of the drug accidentally leaks out of the vein where it is injected, severe irritation and ulceration of the skin and soft tissues can occur.
• Decreased blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications.

**Less Likely**
• A metallic taste in the mouth
• Prickling or tingling of the face
• Sensitivity to light
• Abnormalities of liver and kidney blood tests
• Allergic reactions

**Rare**
• Anaphylaxis (severe allergic reaction)
• Headache
• Seizures
• Blurred vision
• Generalized weakness
• Brain hemorrhage
• Severe liver damage
• Low blood pressure
• Multiple nerve dysfunction

G-CSF (10/18/05)

**Very Likely**
• Redness, swelling, itching, and pain at the injection site
• Mild to moderate muscle/bone aching, which is usually relieved with mild medication such as acetaminophen

**Less Likely**
• Hair loss
• Nausea and/or vomiting
• Diarrhea or constipation
• Loss of appetite, change in taste, and/or weight loss
• Tiredness and/or general weakness
• Indigestion and/or stomach pain
• Mouth sores
• Fever
• Headache
• Difficulty sleeping
• Joint pain
• Swelling of legs
• Dizziness

Rare
• Low oxygen levels in the blood

Thalidomide (6/22/05)

Very Likely
• Constipation
• Tiredness and/or sluggishness
• Weakness
• Bodily discomfort
• Sleepiness and decreased alertness
• Nausea
• Skin rash; itchiness
• Dryness of skin, mouth, eyes, or linings of other body openings or canals open to the air
• Numbness, tingling, or pain in hands or feet caused by damage to the nerves that may be permanent
• Muscle pain
• Heartburn and/or indigestion

Less Likely
• Headache
• Blurry vision
• Muscle weakness
• Trembling or shaking
• Mood changes: depression
• Confusion
• Dizziness
• Swelling of the face, hands, or feet
• Decreased blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications
• Shortness of breath
• Low thyroid level, which can result in tiredness, weakness, lack of interest in sex, and weight gain

Less Likely, but Serious
• Blood clots in the legs, lungs, and brain
• Narrowing and/or blockage of a blood vessel
• Seizures
• Allergic reaction, including drug fever
• Low blood pressure and dizziness (Therefore, you should sit upright for a few minutes before standing up from a reclining position to avoid falling.)
• Change in liver function
Rare
- Decreased coordination while walking
- Slow heart rate
- Severe rash called Stevens-Johnson syndrome, which can cause fever and red sores in your mouth and eyes

Other Risks
- There is an extremely high risk that severe, life-threatening human birth defects will result if a woman becomes pregnant while taking thalidomide, even a single dose.
- 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).
- Women of childbearing potential should not handle or administer thalidomide unless wearing gloves, as it is unknown whether thalidomide is absorbed through the skin. For this reason, the capsules should not be opened.

Do not share thalidomide with anyone and keep out of the reach of children.

Women
Female patients must either not have sexual intercourse or use 2 methods of birth control: one highly active method such as intrauterine device (IUD), hormonal (birth control pills, injections, or implants), tubal ligation, or partner’s vasectomy, AND one additional effective birth control method such as latex condom, diaphragm, or cervical cap, for at least 4 weeks before starting thalidomide therapy, during therapy, and for at least 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 menstrual periods for at least 24 consecutive months.

The patient must not breast-feed a baby while she is being treated with thalidomide. She must NEVER donate blood or ova while she is being treated.

Men
Male patients must use a latex condom every time that they have sexual intercourse with a woman during thalidomide therapy and for 4 weeks after discontinuing thalidomide, even if they have had a successful vasectomy because thalidomide is present in semen or sperm. Men should advise partners with the potential for pregnancy and who may be exposed during the study, to use at least one additional form of birth control. The patient must tell the doctor if he has had sex with a woman without using a latex condom, or if he thinks for any reason that his partner may be pregnant. The patient may NOT be a sperm or blood donor while he is being treated with thalidomide.
**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
  - Tubal ligation
  - Partner’s vasectomy
  - Hormonal (birth control pills, injections, or implants)
  - 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 or feet that may not be reversible) and drowsiness. (If I become drowsy, I will not operate heavy machinery or drive a car. Also, I will avoid alcohol and other medicines not prescribed by my doctor). If I develop a red itchy rash I will contact my doctor immediately. If I feel dizzy, I will sit up right 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 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 and an additional method of birth control 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. In addition to a latex condom, another form of birth control should be utilized.

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

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

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

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

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if she/he has any questions regarding her/his treatment with THALOMID™ (thalidomide) and have answered those questions to the best of my ability. I will ensure that the appropriate components of the patient consent form are completed.

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.

Radiation Therapy (RT)
The risks and discomforts associated with radiation can be divided into early reactions (those happening during or shortly after radiation) and late reactions (those happening well after the completion of radiation). Sometimes after radiation, the skin in the treated area may turn red, blister, and/or peel while you are receiving chemotherapy or just after you have chemotherapy. In general, most radiation reactions (other than fatigue) are limited to the site being treated. For example, if your leg is being treated, you will not feel nauseated from radiation treatment. Your doctor will specifically identify those risks connected with the location of your tumor.
Early RT reactions:

**Very Likely**
- Mild (*slight redness*) to severe (*painful skin blistering*) skin reactions; may become most noticeable during chemotherapy. The combination of radiation and doxorubicin may result in more severe side effects, especially in skin reactions such as scar tissue.
- Tiredness
- Reduction in blood counts, possibly resulting in bleeding or infection
- Diarrhea (*if abdominal wall is treated*)
- Wound healing delay after surgery

Late RT Reactions:

**Very Likely**
- Skin in the treated area may appear tanned and may stay this way for a number of years after radiation.
- Tissues in the treated area may feel hard and woody: If this occurs, it is likely to be permanent.
- Pain in a treated limb: This symptom may occur one to several years after completion of treatment and may last for many years.
- Swelling: This may occur in the first year after treatment. In many patients this will go away. Some patients will have persistent swelling and will need to use elastic stockings. If severe, you may require the use of a pump that pushes swelling out of the extremity. Some patients will notice temporary swelling after strenuous activity.
- Bones more susceptible to fracture.
- Irradiated skin, especially over the shin and elbow, may heal more slowly if injured or bruised.

**Less Likely, but Serious**
- Injury to the bowel (*if abdominal wall is treated*)
- If heart, lung, liver, or stomach are in the field of treatment, these organs could be damaged.

**Rare**
- Injury to the spinal cord (*if the back area is treated*)
- Radiation can cause tumors in the irradiated tissues. This is rare (*1 in 2,000*) in adults but can occur many years after treatment.

**Surgery**
Complications may occur when tumors are removed from the legs, arms, and body wall whether or not radiation or chemotherapy is given. While surgical treatment of these tumors results in wound healing delay or infection, the addition of radiation or radiation and chemotherapy may increase this problem. Ultimately, most patients will heal satisfactorily. Risks, which may be associated with surgical procedures in this study, are described below:

**Patients with tumors of arms or legs**

**Likely**
- Decreased function of affected limb because of muscle, nerve, or skin damage

**Less Likely, but Serious**
- Treatment of large tumors with radiation and surgery or radiation, chemotherapy, and surgery may result in infection or lack of healing, which could result in prolonged hospitalization and rarely, amputation.

**Patients with tumors of the abdominal wall**
Radiation and surgery or radiation, chemotherapy, and surgery for tumors of the abdominal wall may result in failure of the wound to heal and occasionally the development of a hernia (*projection of*...
organ or part through wall that normally holds it). If the removal of the abdominal wall sarcoma is very large, it may be necessary to replace the abdominal wall with a plastic material. While this standard surgical procedure usually works well to reinforce or reconstruct body tissues, it may result in wound infection and prolonged hospitalization.

Patients with tumors of the chest wall
Removal of tumors that involve the chest wall require removal of at least part of the bones that are part of the chest. To repair this, a standard surgical procedure involving the use of plastic material to reinforce or reconstruct body tissues may be required. Again, this may uncommonly result in a severe infection. Should this repair break down, the lung could be open to the air. Other methods of repair would then be needed.

With any operation, there is always the risk of complications related to associated heart disease, lung disease, diabetes etc. Pre-existing problems such as these may place you at increased risk for having heart or lung problems during surgery. Rarely, these complications may result in death.

Reproductive Risks (See Thalidomide Risks for additional important reproductive risks.)
If you are a woman able to have children and have not been surgically sterilized (hysterectomy or postmenopausal for 24 consecutive months), you must use adequate birth control approved by your doctor. If you are unwilling to use this form(s) of birth control, you should not participate in this study. Because the treatments in this study can affect an unborn baby, you should not become pregnant while on this study. For this reason, you also are not eligible to participate in this study if you are pregnant. If you should become pregnant while you are on this study, you must tell your doctor immediately. If you have an infant, you should not nurse your baby while on this study. If you have any questions about the reproductive issues or about preventing pregnancy, please discuss them with your doctor or a member of the Study Team.

Male patients on this study must use a latex condom every time they have sexual intercourse with a woman. If you are unwilling to use this form of birth control, you should not participate in this study. If you have caused anyone to become pregnant while you are on this study, you must tell your doctor immediately.

Your physician will be checking you closely to see if any of these side effects are occurring. Routine blood tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

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. The addition of thalidomide to radiation and/or chemotherapy and surgery may be more effective in treating your cancer, but that benefit cannot be guaranteed. We hope the information learned from this study will benefit other patients with soft tissue sarcoma in the future.

WHAT OTHER OPTIONS ARE THERE? (7/21/04)
You may choose to not participate in this study. The use of thalidomide to treat soft tissue sarcoma is experimental, and this treatment is not available unless you are participating in a research study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; (4) no treatment except medications to make you feel better.
With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

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), qualified representatives of applicable drug manufacturers including Celgene Corporation, RTOG, and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS? (7/21/04)**

The Division of Cancer Treatment, and Diagnosis, NCI will provide you with the thalidomide free of charge for this study. Every effort will be made to ensure adequate supplies of the thalidomide, free of charge, for all participants. If the drug becomes commercially available for this indication there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should this situation arise. You will receive no payment for taking part in this study.

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

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

**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 group of experts in sarcoma from the RTOG sarcoma committee, the study chairs, and the study statistician will be reviewing the data periodically throughout the study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

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

__________________________    ________________________
Name       Telephone Number

For information about this study, you may contact:

__________________________    ________________________
Name       Telephone Number

For information about your rights as a research subject, you may contact:
(OPRR 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 at
  http://www.cancer.gov/clinicaltrials
  
or
  for accurate cancer information including PDQ (Physician Data Query) visit
  http://www.cancer.gov/cancerinfo/pdq

SIGNATURE

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

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

__________________________   ________________________
Patient Signature (or legal Representation)       Date

__________________________   ________________________
Name of Person Obtaining Consent       Signature       Date
ABOUT USING TISSUE FOR RESEARCH

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

In addition, we would like to keep some of the tissue that is leftover for future research, as well as some blood samples. If you agree, your tissue and/or blood will be kept and may be used in research to learn more about cancer and other diseases.

ABOUT USING BLOOD FOR RESEARCH (7/21/04)

You are being asked for permission to send an additional small amount of your blood to a central office for future research. Your blood will be drawn at 5 treatment time points. These samples (about 1 ½ teaspoonsfuls each) of your blood will be sent to the central office and may be used to learn more about cancer and other diseases.

The research that may be done with your tissue/blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue/blood before it is given to a researcher. Reports about research done with your tissue/blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue or to use your blood for future research is up to you. **No matter what you decide to do, it will not affect your care or your participation in this study.**

If you decide now that your tissue/blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue/blood and then any tissue/blood that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee and/or that we dispose of your blood.

In the future, people who do research may need to know more about your health. While [doctor/institution] may give researchers reports about your health, your doctor/institution will not give researchers your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue/blood is used for genetic research (about diseases that are passed on in families). Even if your tissue/blood is used for this kind of research, the results will not be put in your health records.
Your tissue/blood will be used only for research. However, the research done with your tissue/blood may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be financially compensated.

**BENEFITS**

The benefits of research using tissue/blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**RISKS**

**Physical Risks**

Most patients will heal satisfactorily after having surgery or a needle biopsy to remove tissue. Risks and side effects of a biopsy/surgery can include bleeding, pain, delayed healing, possible infection, and rarely, creation of an abnormal opening or passage.

If your blood is drawn, you may experience some discomfort, bruising, and/or bleeding at the site of the needle insertion. Occasionally, some people experience dizziness or feel faint. In rare instances, infection may develop at the site of the needle insertion.

**Social-Economic Risks**

There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _________ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, 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.

**MAKING YOUR CHOICE**

You may choose not to take part or to terminate your participation in this part of the study at any time. Leaving this part of the study will not result in any penalty or loss of benefits to which you are entitled.

If you have any questions about the research involving your tissue/blood or about this form, please talk to your doctor or nurse, or call the institution’s research review board at ___________ (IRB’s phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care or your participation in this study.**

1. My tissue and/or blood may be kept for use in research to learn about, prevent, or treat cancer.
   
   Yes  
   No  

2. My tissue and/or blood may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   
   Yes  
   No  

3. Someone from _________ (doctor’s office/institution) may contact me in the future to ask me to take part in more research.
   
   Yes  
   No
**Participant statement:**
I have read and received a copy of this consent form. I have been given an opportunity to discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

<table>
<thead>
<tr>
<th>Patient’s Name</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

**Witness statement:**
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient’s signature.

<table>
<thead>
<tr>
<th>Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

NEW YORK HEART ASSOCIATION CLASS DEFINITIONS

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Cardiac Symptoms</th>
<th>Limitations</th>
<th>Need for Additional Rest*</th>
<th>Physical Ability to Work**</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Full Time</td>
</tr>
<tr>
<td>II</td>
<td>Only moderate</td>
<td>Slight</td>
<td>Usually only slight or occasional</td>
<td>Usually full time</td>
</tr>
<tr>
<td>III</td>
<td>Defined, with less than ordinary activity</td>
<td>Marked</td>
<td>Usually moderate</td>
<td>Usually part time</td>
</tr>
<tr>
<td>IV</td>
<td>May be present even at rest, &amp; any activity increases discomfort</td>
<td>Extreme</td>
<td>Marked</td>
<td>Unable to work</td>
</tr>
</tbody>
</table>

*To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.
Grade and TNM definitions

**Tumor grade (G)**
- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated

**Primary tumor (T)**
- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Tumor 5 cm or less in greatest dimension
  - T1a: Superficial tumor
    - Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or superficial and beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.
  - T1b: Deep tumor
- T2: Tumor more than 5 cm in greatest dimension
  - T2a: Superficial tumor
  - T2b: Deep tumor

**Regional lymph nodes (N)**
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

**Distant metastasis (M)**
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

**Stage I**
- G1-2, T1a, N0, M0
- G1-2, T1b, N0, M0
- G1-2, T2a, N0, M0
- G1-2, T2b, N0, M0
Stage II
- G3-4, T1a, N0, M0
- G3-4, T1b, N0, M0
- G3-4, T2a, N0, M0

Stage III
- G3-4, T2b, N0, M0

Stage IV
- Any G, any T, N1, M0
- Any G, any T, any N, M1
APPENDIX IV
RTOG 0330
REPORTING FORM FOR CIRCULATING FACTOR

Patient RTOG ID#: ______________________ Case #________

Institution Name: ________________________

Date of Collection: _______________________

Institution Phone Number: ________________

Type of Specimen: _______________________

Circle the time point for the specimen being submitted.

**Cohort A:**

a. pre-treatment

b. end of 2nd course of RT/thal.

c. day starting post-op adjuvant thal.

d. 3 mo. on post-op adjuvant thal.

e. 3 mo. following completion of post-op adjuvant thal.

**Cohort B:**

a. pre-treatment

b. week four of pre-op RT/thal.

c. day starting, post-op adjuvant thal.

d. 3 mo. on post-op adjuvant thal.

e. 3 mo. following completion of post-op adjuvant thal.

**Send to:**

James C. Watson, MD
Fox Chase Cancer Center
7701 Burholme Avenue, Room C403
Philadelphia, PA 19111
(215-214-1437)
APPENDIX V
FEDERAL REGULATIONS FOR MINOR ASSENT

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
PART 50--PROTECTION OF HUMAN SUBJECTS--Table of Contents
Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of dire

Any clinical investigation within the scope described in Secs. 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds and documents that:
(a) The risk is justified by the anticipated benefit to the subjects;
(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in Sec. 50.55.

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
PART 50--PROTECTION OF HUMAN SUBJECTS--Table of Contents
Subpart D--Additional Safeguards for Children in Clinical Investigations

Sec. 50.55 Requirements for permission by parents or guardians and for assent by children.
(a) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent.
(b) In determining whether children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.
(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:
   (1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or
   (2) That the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:
   (1) The clinical investigation involves no more than minimal risk to the subjects;
   (2) The waiver will not adversely affect the rights and welfare of the subjects;
   (3) The clinical investigation could not practicably be carried out without the waiver; and
   (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine that the permission of each child's parents or guardian is granted.
   (1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under Sec. 50.51 or Sec. 50.52.
   (2) Where clinical investigations are covered by Sec. 50.53 or Sec. 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by Sec. 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.
APPENDIX VI

MINOR ASSENT ADDITION TO THE CONSENT FORM SIGNED BY THE PARENTS

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0330

A PILOT PHASE II STUDY OF PRE-OPERATIVE RADIATION THERAPY AND THALIDOMIDE (IND 48832; NSC 66847) FOR LOW GRADE PRIMARY SOFT TISSUE SARCOMA OR PRE-OPERATIVE MAID/THALIDOMIDE/RADIATION THERAPY FOR HIGH/INTERMEDIATE GRADE PRIMARY SOFT TISSUE SARCOMA OF THE EXTREMITY OR BODY WALL

I have had this study and consent form explained to me in a way that I understand. I have had a chance to ask questions and have them answered to my satisfaction. I agree to take part in this study.

Signature of Minor Patient:________________________________________
Date: __________________

Signature of Investigator:________________________________________
Date: __________________