RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-14

A PHASE II STUDY OF NEOADJUVANT CHEMOTHERAPY AND RADIATION THERAPY IN THE MANAGEMENT OF HIGH-RISK, HIGH-GRADE, SOFT TISSUE SARCOMAS OF THE EXTREMITIES AND BODY WALL

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SCHEMA

RECORD	**Tumor Location**	**RESTER**	**Treatment**
	1. Lower extremity *(including hip)*		Neoadjuvant chemotherapy x 3 cycles with concurrent RT followed by surgical resection and an additional three cycles of chemotherapy +/- RT Boost
	2. Upper extremity *(including shoulder)*		
	3. Body wall		

Neoadjuvant Chemotherapy *(MAID)*

Mesna 2500 mg/m^2/day as a continuous intravenous infusion via a peripheral line Days 1-4
(Optional: the same dose of Mesna can be given over 12 hours on day 4 only)
Doxorubicin 20 mg/m^2/day as a continuous intravenous infusion via a central line Days 1-3
Ifosfamide 2500 mg/m^2/day as a continuous intravenous infusion via a peripheral line Days 1-3
DTIC 225 mg/m^2/day as a continuous intravenous infusion via a central line Days 1-3
G-CSF 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)*.

Repeat every 3 weeks x 3 cycles preoperatively, then again beginning 3-5 weeks after the resection for 3 additional cycles. See Section 8.7 for timing of surgery.

Concurrent Radiation Therapy

Two RT cycles of 22 Gy in 11 fractions in 13-15 days starting three days after each of the first two cycles of preoperative chemotherapy, total dose 44 Gy.

Postoperative Radiation Therapy *(for Positive Margins)*

Starting 14 days after surgery assuming wound healing is good, 16 Gy will be given by external beam *(2 Gy x 8 fractions)*. Patients with negative surgical margins will not receive boost.

ELIGIBILITY: *(See Section 3.0 for details)*

- Histologically confirmed, locally confined, soft tissue sarcomas, Grade 2 or 3 and measures = 8 cm.
- No evidence of metastases
- Age ≥ 18 years; KPS ≥ 80
- Treatment must begin within two weeks after registration
- Normal heart function *(EF ≥50%)*
- WBC ≥ 4,000, platelets ≥ 150,000, bilirubin ≤ 1.5, creatinine ≤ 1.5, SGOT ≤ 50.
- No prior chemotherapy, irradiation, or biotherapy

Required Sample Size: 30 + 30 = 60 (9/8/98)

RTOG Institution # _____

RTOG Case # _____ *(page 1 of 2)*

ECOG Seq. # _____

_____(Y)	1.	Is the malignancy a primary or recurrent *(after surgery only)* soft tissue sarcoma?
_____(2-3)	2.	What is the grade *(AJCC Stage)*?
_____(Y)	3.	Was histologic confirmation *(biopsy)* done within 2 months prior to registration?
_____	4.	What is the location of the sarcoma (*upper extremity, lower extremity, body wall)*?
_____(Y)	5.	Is the lesion equal or greater than 8 cm?
_____(≥ 18)	6.	What is the patient's age?
_____(≥ 80)	7.	What is the KPS?
_____(Y)	8.	Have all required tests been performed within the time frame specified in Section 4.0?
_____(N)	9.	Is there any evidence of metastatic disease?
_____(N)	10.	Are there any contraindications to surgery?
_____(N)	11.	Has the patient received any prior radiation, chemotherapy, or biotherapy?
_____(Y/N)	12.	Has the patient had a previous malignancy other than adequately treated non-melanoma skin cancer or cervical cancer *in-situ*?
		_____(Y) If yes, has the patient been disease free for ≥ 5 years?
_____(N/NA)	13.	Is the patient pregnant, lactating or not using effective contraception? *(code NA for men and for females without child-bearing potential)*
_____(N)	14.	Does the patient have an active uncontrolled bacterial, viral, or fungal infection?
_____(N)	15.	Does the patient have any serious medical or psychiatric illness which would prevent informed consent or limit survival to less than 2 years?
_____(Y)	16.	Has a study-specific consent been signed?
_____(≥ 4)	17.	What is the WBC *(per 1000)*?
_____(≥ 150)	18.	What is the platelet count *(x 1000)*?
_____(≤ 1.5)	19.	What is the bilirubin?

(continue to page 2)

RTOG Institution # _____

RTOG 95-14/ECOG R9514 **ELIGIBILITY CHECK** ***(STEP 1) (9/8/98)***

RTOG Case # _____ *(page 2 of 2)*

ECOG Seq. # _____

_____(≤ 1.5) 20. What is the creatinine?

_____(≤ 50) 21. What is the SGOT?

_____(N) 22. Does the patient have any known hypersensitivity to *e-coli* derived proteins?

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # *(if different)*

_____ Medical Oncologist

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code *(9 digit if available)*

_____ Method of Payment

_____ Will any care be given at a VA or military facility?

_____ Treatment Start Date *(must be after registration)*

_____ Treatment Assignment

Completed by _____ Date _____

RTOG Institution # _____

RTOG 95-14/ECOG R9514 **ELIGIBILITY CHECK** ***(STEP 2)***

RTOG Case # _____

ECOG Seq. # _____

_____(Y/N) 1. Is patient continuing on to the second step? ***(If no, call to RTOG HQ must still be made)***

_____(N) 2. Is there evidence of progression, second primary or metastatic disease?

_____(Y) 3. Has surgery been done?

_____(Y/N) 4. Are all margins negative?

Yes: Arm 2 *(Post Op Chemo Alone for negative margins)*

No: Arm 3 *(Post Op Chemo and RT for positive margins)*

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # *(if different)*

_____ Date of Surgery

Completed by _____ Date _____

1.0 INTRODUCTION

Soft tissue sarcomas are uncommon malignancies. It is estimated that 6,000 cases will have occurred in 1994 .[1] This constitutes approximately 0.6% of all invasive cancers diagnosed per year in the United States. At each anatomic site in the body, there are small numbers of a variety of histopathological types of soft tissue sarcomas. Approximately 60% of soft tissue sarcomas occur in the lower extremity and torso, with the remaining 40% being distributed throughout the remainder of the body. In recent years, rapidly evolving treatment strategies have generated considerable interest in the management of these relatively uncommon tumors.[2] Historically, radical surgical resection has been the treatment of choice for soft tissue sarcomas. Enneking and Shiu from the University of Florida and Memorial Sloan Kettering Cancer Center have achieved some of the very best results using resection alone, with local recurrence rates of 17% and 18%, respectively.[2,3] However, this was achieved with an amputation rate of 54% and 42%, respectively. Recent results of surgery alone have been local control of 66% at Memorial Hospital[4] and 69% at Milan.[5] It is now generally accepted that limb salvage efforts should include surgery in combination with other modalities, especially preoperative or postoperative radiation therapy.[6] The rationale for combining radiation and surgery is that sarcomas, especially high grade sarcomas, infiltrate the grossly normal appearing tissue adjacent to the evident lesion. Thus, removal of the gross lesion by simple excision is followed by local recurrence in 70-90% of patients.[7] Simple resection was replaced by radical resection so that the surgical margins would include a wide margin of grossly normal tissue around the tumor.[3,6] Radiation at moderate dose levels *(50-55 Gy)* should be effective in eradicating the microscopic extensions beyond the gross lesion. In other words, moderate dose radiation and relatively conservative surgery would accomplish the same as the expansion from simple to radical surgery. This has been accomplished in a number of centers with low amputation rates and has been an effective method of limb salvage.[8-11]

The experience to date in the clinical setting has supported these experimental findings. Two hundred fifty-eight patients treated with wide resection and preoperative or postoperative radiation therapy have been reported by Suit and his co-workers from the Massachusetts General Hospital *(MGH)* from 1971-1985.[12] The five-year local control rate in postoperative and preoperative groups were 86% and 91%, respectively. The local success rate has been improved recently. Between 1980 and 1986, local control rates were 92% and 97% for patients treated postoperatively *(63 patients)* and preoperatively *(82 patients)*, respectively. In this non-randomized trial, there appeared to be an advantage with the use of preoperative radiation therapy, especially for larger lesions. This is also supported by work published by Barkley and co-workers at the M.D. Anderson Hospital.[13] Their experience also indicates an advantage with regard to local control in patients receiving preoperative radiation therapy compared to those receiving postoperative radiation therapy. In their series of 110 patients, the local recurrence rate was 10% in patients receiving preoperative radiation therapy versus 20% in those patients receiving postoperative radiation therapy, and local control and disease-free survival rates were higher for patients whose sarcomas were Stage 1A, 2A or 3A. For Stage 2B and 3B tumors, local control was impressively higher for patients treated preoperatively. Disease-free survival was low for Stage 2B and 3B patients; thus, 50% loss was due principally to distant metastases. Barkley has also found a correlation between survival and size and grade of sarcomas. For 13 patients whose sarcomas were less than 5 cm, the survival at 66 months was 90%. For patients whose sarcomas were 5-15 cm, the survival was about 60%, but only 45% of patients with sarcomas >15 cm in diameter survived.

In both the MGH and M.D.Anderson series there have been problems with delayed wound healing. This has been especially true for elderly obese patients with large sarcomas of the proximal medial thigh. Wound complications may also occur in patients treated by surgery alone.[14] When this occurs for the patient who is scheduled for postoperative radiation treatment, the residual tumor may recur grossly before treatment can be started because of the wound morbidity.

Chemotherapy has been used in an effort to improve both local control and systemic control in patients with soft tissue sarcomas. Eilber and Morton have been strong proponents of a program which has consisted of intra-arterial adriamycin followed by rapid fraction radiation therapy and subsequent local excision.[15] Their data has consistently shown local recurrence rates of ≤ 10% with survival rates of 74% in Stage 3 tumors. They have since shown that it is not necessary to provide the adriamycin by an intra-arterial route.

Chemotherapy has been assessed extensively as a means of improving survival in patients with locally limited disease. Most studies assessing adjuvant chemotherapy in the management of soft tissue sarcomas have not demonstrated a significant improvement in survival.[16-20] Many have demonstrated that chemotherapy given for the purpose of improving survival has improved disease-free survival and local control. A combination of ifosfamide with mesna, doxorubicin and dacarbazine has resulted in response rates as high as 47% with complete response rates as high as 10%.[21,22] In spite of this, progress has not been made toward the development of effective adjuvant

chemotherapy strategies for soft tissue sarcoma. Metastasis occurs in up to half of all patients, even with adequate local control.[23,24] Most hematogenous metastases are to the lung. The frequency with which distant failure occurs is directly proportional to the size of the primary tumor in patients with high grade soft tissue sarcomas. A recent abstract describing a meta-analysis of 13 randomized trials of adjuvant chemotherapy versus control in soft tissue sarcomas demonstrated that chemotherapy increases overall survival by 9% with both distant and local recurrence rates being reduced.[25] There has been progress in the application of chemotherapy. There has been a considerable interest focused on the ability to maintain dose intensity of chemotherapy using colony-stimulating factors to alleviate myelosuppression. Granulocyte-macrophage *(GM-CSF)* has been used with a variety of regimens to help maintain dose intensification. In a few studies this has resulted in improved response rates.[26]

Recently, investigations at Massachusetts General Hospital have evaluated MAID and radiation in soft tissue sarcoma of the extremity.[27] They have begun a phase II trial evaluating the efficacy of preoperative chemotherapy with Mesna, Adriamycin, Ifosfamide and Dacarbazine *(MAID)* and radiation, followed by resection and postoperative radiotherapy and chemotherapy.

Adult patients with AJCC stage IIB or IIIB extremity soft tissue sarcomas ≥ 8 cm were treated with MAID chemotherapy for five days. Following a two-day rest, radiation therapy to 22 Gy was delivered in 11 fractions. After two days, this chemo/radiation cycle was repeated, bringing the preoperative radiation dose to 44 Gy and the number of chemotherapy cycles to three. After a three-week rest, surgical resection was performed. If surgical margins were positive, an additional 16 Gy boost was delivered in eight fractions, followed by three additional chemotherapy cycles.

A total of 26 patients who were clinically MO at entry have completed treatment on this protocol and have been compared with matched historical controls. The median follow up for these patients is 13 months *(range 3-76 months)*. Pathologic response rates measured as post-treatment percent tumor necrosis, have varied from 10 to 100% with mean and median values of 84% and 96%. The local control, disease-free survival and overall survival of these patients has been compared to a control group of 32 patients matched historically for tumor size, grade, age, and era of treatment. The actuarial five-year local control, disease-free survival rate and overall survival rate for MAID patients is 100%, 84% and 93% respectively. For the control group these rates are 97, 45 and 60%, respectively. Following a course of aggressive chemotherapy and radiation therapy, 84% of patients with high risk soft tissue sarcoma are free of disease at five years compared to 45% of patients treated without chemotherapy. Despite a short follow-up time, these results are encouraging.

Complications of chemotherapy are shown in Table 1. Eight patients developed grade 4 *(Cooperative Group Common Toxicity Criteria, [CGCTC])* neutropenia, including five patients with neutropenic fevers. One of these five developed a life-threatening sepsis after the third cycle of chemotherapy but went on to complete her surgery and chemotherapy. Five patients experienced non neutropenic fevers requiring discontinuation of dacarbazine *(DTIC)* in two patients after the fourth cycle. Two other patients had dose reductions secondary to weight loss. Microscopic hematuria was seen in 16 of 26 patients although none developed gross hematuria. Nausea and vomiting was tolerable in most patients and when severe resolved several days after completion of the chemotherapy cycle. One patient developed a port-a-cath infection requiring revision while a second patient developed a biopsy-proven idiopathic pulmonary inflammatory reaction after the 3rd cycle of chemotherapy.

Table 1
Chemotherapy Toxicity

	Cooperative Group Grade				
	0	1	2	3	4
Neutropenia	2	3	6	7	8
Thrombocytopenia	9	10	3	2	2
Hemoglobinemia	1	1	11	10	3
Nausea	0	7	14	5	-
Vomiting	2	4	18	2	0

Microscopic Hematuria	16	1	0	0	0

	Frequency
Neutropenic Fevers	5
Non Neutropenic Fevers	5
Sepsis	1
Other	2

Acute skin reactions were common. Radiation Therapy Oncology Group *(RTOG)* acute morbidity scoring criteria showed: 8 patients with grade 3/4 reactions *(confluent moist desquamation)*, 5 with grade 2/4 reactions *(tender, patchy moist desquamation)* and 13 with grade 1/4 reactions *(dry desquamation)*. Most patients with grade 3/4 toxicity had reactions which peaked during the third cycle of chemotherapy *(i.e. after completion of radiation therapy)*. A small number of patients exhibited these reactions during the second chemotherapy cycle. Patients with grade 3/4 reactions were managed conservatively with narcotics *(if indicated)* and burn care. All grade 3/4 acute skin reactions subsided in the three-week interval before surgery.

Wound complications are shown in Table 2. A total of nine patients experienced a delay in the healing of the surgical wound. Seven of these nine were managed conservatively on an outpatient basis. Three patients developed a wound infection as a component of their wound healing delay. Two of these three were managed as outpatients while one required admission for intravenous antibiotic therapy. The one patient requiring surgery developed thrombus in a synthetic *(PTFE)* vascular graft in the immediate postoperative period. This patient required multiple vascular procedures and eventual plastic surgery reconstruction. In addition, to early wound complication, two patients developed late complications. One patient suffered a fall 8 months after surgery and required open reduction with internal fixation for a pathologic fracture of an osteoallograft. A second patient developed an acute arterial *(femoral)* occlusion 29 months after surgery requiring two separate by pass procedures.

Table 2
Early Wound Complications

Complication	*Frequency*
Wound Healing Delays	9/26
Wound Infection	3/9
Requiring Hospitalization	3/9
Requiring Surgery	1/9
Other	2/26
(2 patients with DVT perioperatively)	

On the basis of this data and a recent report of an indiviual patient data meta-analysis of all randomized prospective trials which demonstrated a small but real benefit for patients receiving adriamycin based chemotherapy, we have proposed to repeat the work of the MGH group in a phase II Intergroup environment.[28]

2.0 OBJECTIVES

2.1 To assess whether patients treated with MAID chemotherapy interdigitated with preoperative radiation therapy in the cooperative group setting have toxicity, response rate and complications which are comparable to that in the MGH pilot data.

2.2 To follow patients for local control and local complications related to surgery and neoadjuvant therapies.

2.3 To develop a tissue repository of frozen soft tissue sarcoma for ancillary genetic and flow cytometric analysis of these tumors.

2.4 To form an Intergroup Working Sarcoma Group which will develop a patient base, relationships and support to develop and complete a phase III study of adjuvant therapy in STS in the future.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have a primary or recurrent *(post surgery)* soft tissue sarcoma confirmed by study pathologist as grade 2 or 3. Biopsy must be done within 2 months prior to registration.

3.1.2 Sarcoma located on the upper *(includes shoulder)* or lower *(includes hip)* extremities or on the body wall.

3.1.3 AJC Stage IIB and IIIB *(≥ 8 cm)* will be included in this study *(see Appendix III)*.

3.1.3.1 On preoperative chest CT scans, patients may have ≤ 4 chest lesions that are all ≤ 3 mm in diameter each and still be eligible for this protocol. This is done because of the propensity of most patients over 60 to have some parenchymal lesions which are not pathologic.

3.1.4 Age ≥ 18.

3.1.5 Karnofsky performance status should be ≥ 80%.

3.1.6 WBC ≥ 4,000, platelets ≥ 150,000, bilirubin ≤ 1.5, creatinine ≤ 1.5, SGOT ≤ 50.

3.1.7 Normal heart function *(study of EF ≥ 50% within past six months)*.

3.1.8 Treatment must begin within two weeks after registration.

3.1.9 Patients must use effective contraception; must not be pregnant or lactating.

3.1.10 No evidence of metastases

3.1.11 No contraindications to surgery

3.1.12 Patient must sign a study-specific informed consent form prior to registration.

3.2 Ineligibility Criteria

3.2.1 Prior treatment with radiation, chemotherapy, or biotherapy.

3.2.2 Histopathology is rhabdomyosarcoma, extraosseous Ewing's, primitive neuroectodermal tumors, osteosarcoma or chondrosarcoma, Kaposi's sarcoma or angiosarcoma of the scalp/face, any sarcoma of the head and neck.

3.2.3 No prior or concurrent malignancies other than surgically treated carcinoma *in situ* of the cervix and squamous or basal cell carcinoma of the skin are allowed within the preceding five years.

3.2.4 Patients may have no serious medical or psychiatric illness which would prevent informed consent or limit survival to less than two years.

3.2.5 Congestive heart failure or myocardial infarction within previous six months.

3.2.6 LVEF ≤ 50% or any cardiovascular abnormality resulting in a New York Heart Association functional status ≥ 2 *(see Appendix II)*.

3.2.7 Active uncontrolled bacterial, viral or fungal infection until these conditions are corrected or controlled.

3.2.8 Patients with known hypersensitivity to E-coli derived proteins.

4.0 PRETREATMENT EVALUATIONS

4.1 Prestudy blood tests to be done within two weeks prior to registration; imaging studies to be done within four weeks prior to registration.

4.1.1 History and physical examination with special attention to measures of primary tumor.

4.1.2 Diagram of tumor.

4.1.3 Plain films and MRI or computorized tomography *(CT)* of involved extremities prior to biopsy. CT is adequate for tumors of torso.

4.1.4 PA and lateral CXR.

4.1.5 CT scan of chest prior to registration in protocol.

4.1.6 CBC, differential and platelet count, PTT, PT, SGOT/alkaline phosphatase, serum creatinine, total bilirubin.

4.1.7 EKG; pregnancy test as applicable.

4.1.8 Echocardiography or MUGA scan to evaluate LVEF.

5.0 REGISTRATION PROCEDURES

5.1 First Registration *(Option1)*

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at *(215)* 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to the treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Tumor Location
- Demographic Data

- Treatment Start Date

5.2 Second Registration *(Options 2 and 3)*

5.2.1 The second registration process requires a second phone call to the RTOG Group Office for all patients *(see Section 5.1)* at which time the following information must be provided:

- Institution Name and RTOG number
- Patient Name and the RTOG Assigned Case Number
- Tumor Status *(progression vs. no progression)*
- Eligibility Information for Second Registration
- Date of Protocol Surgery
- Surgical Margins *(negative vs. positive)*

5.2.2 Patients whose tumor has not progressed will be assigned an option number reflecting their subsequent treatment plan. A confirmation of second registration and a new data collection calendar will be mailed to the institution confirming the following treatment options.

Option 2 - *(Negative margins post operatively)*
Patients will receive three additional cycles of chemotherapy according to Section 7.1.3.

Option 3 - *(Positive margins post operatively)*
Patients will receive post-op radiation therapy and three additional cycles of chemotherapy according to Sections 6.3 and 7.1.3.

5.2.3 Patients reported to have tumor progression at the second registration call will not be assigned a new option number and will be designated as "discontinued". The original data collection calendar will be followed.

5.3 ECOG Members *(First and Second Registrations)*

For ECOG institutions, a signed HHS-310 Form, a copy of the institution's IRB approved informed consent document, and written justification for any changes made to the suggested informed consent in this protocol must be on file at the ECOG Coordinating Center before an

ECOG institution may enter patients. The signed HHS 310, institution's informed consent, and investigators justification for changes will be submitted to the following address:

ECOG Coordinating Center
Frontier Science
ATTN: IRB
303 Boylston Street
Brookline, MA 02146-7648
FAX *(617)* 632-2990

Patients must not start protocol treatment prior to registration. The eligibility checklist should be completed and signed prior to calling for registration. To register eligible patients on study, the investigator will telephone the Randomization Desk at the ECOG Coordinating Center at *(617)* 632-2022, Monday-Friday, between the hours of 8:30 am and 4:30 pm EST to allow time to call RTOG that same day. **ECOG members should not call RTOG directly.** The following information will be requested: *a) Protocol Number; b) Investigator Identification (including institution and/or affiliate name and investigator's name);* c) Patient identification *(including patient's name or initials, chart number, social security number and demographics [sex, birth date, race, nine-digit zip code and method of payment]);* d) Eligibility Verification; e) Any additional information listed in Section 3.0. Patients must meet all of the eligibility requirements listed in Section 3.0. The randomization specialist will verify eligibility by asking questions from the checklist, and will also verify IRB approval. RTOG will forward a confirmation of treatment assignment to the ECOG Randomization Desk for routing to the ECOG participating institution.

Note: A patient may be canceled only if no protocol therapy is administered. Written notification and an explanation must be received at ECOG as soon as this has been determined. ECOG pateints, even if discontinuing treatment msut be registered to Step 2 *(Section 5.2)* by contacting the ECOG Coordinating Center. RTOG will notify ECOG if the patient may be canceled. Once a patient has been given protocol treatment, all forms must be submitted.

6.0 RADIATION THERAPY

6.1 General Guidelines

6.1.1 In general, the entire compartment need not be covered. If a margin of 12 cm 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.

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 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.

6.2 Preoperative Radiation Therapy

6.2.1 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 cycles 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 pre-operative irradiation dose will be 44 Gy in 22 fractions.

6.2.2 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 margins beyond clinically or radiologically evident sarcoma will be 9 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.

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

6.3 Post-Operative Radiation Therapy.

6.3.1 Postoperative 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. Chemotherapy can resume thereafter.

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.

7.0 DRUG THERAPY *(MAID)*

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

TX	Cycle 1 Days	RT* Days	Cycle 2 Days	RT Days	Cycle 3 Days	Surg Day	Cycle 4 Days	Cycle 5 Days	Cycle 6 Days
Mesna	1-4		22-25		43-46		101-104	122-125	143-146
Dox	1-3		22-24		43-45		101-103	122-124	143-145
Ifos	1-3		22-24		43-45		101-103	122-124	143-145
DTIC	1-3		22-24		43-45		101-103	122-124	143-145
RT		7-20		28-41					
Surgery						80			

* 11 treatments in 13-15 days.

7.1 Dose

7.1.1 *Preoperative Chemotherapy*

Patients will receive a maximum of six cycles of MAID chemotherapy. Three cycles will be administered preoperatively interdigitated with radiation therapy and three cycles will be administered postoperatively. The postoperative chemotherapy *(Section 7.1.3)* should be instituted between 21-35 days following surgery. Delays beyond 35 days will be considered a major protocol deviation.

7.1.1.1 *Mesna*: 2500 mg/m^2/day as a continuous intravenous infusion administered via a peripheral line for 4 days starting on day 1 of the drug cycle and repeated on day 22 *(provided patients have recovered from their toxicities)*. Optional: the same dose of Mesna could be given over 12 hours on day 4 only.

7.1.1.2 *Doxorubicin*: 20 mg/m^2/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 *(provided patients have recovered from their toxicities)*.

7.1.1.3 *Ifosfamide*: 2500 mg/m^2/day as a continuous intravenous infusion administered via a peripheral line for 3 days starting on day 1 of the drug cycle and repeated on day 22 *(provided patients have recovered from their toxicities)*.

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

7.1.1.4 *DTIC*: 225 mg/m^2/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 *(provided patients have recovered from their toxicities)*.

7.1.1.5 G-CSF: 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 patients receiving G-CSF, white blood cell counts and differenitial counts should be checked at least twice weekly until the G-CSF is discontinued.

7.1.2 *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)*.

7.1.3 *Postoperative Chemotherapy*

Patients who have had stable disease, or a minor or major clinical response to chemotherapy *(including radiation therapy)* will receive three cycles of treatment in the postoperative period. Postoperative chemotherapy should begin between 21-35 days after surgery. Each cycle of chemotherapy will include mesna, doxorubicin, ifosfamide, DTIC and G-CSF exactly as given in the preoperative period.

7.2 Mesna *(Mesna)*

7.2.1 *Dose Formulation*: Mesna is available as an injectable sterile preservative-free aqueous solution. The colorless solution is supplied in clear glass ampules containing 4 and 10 ml of a 100 mg/ml solution. Mesna may be further diluted in 5% dextrose, 5% dextrose and 0.45% normal saline or normal saline to a final concentration of 1 to 20 ml. Mesna should be given as a continuous intravenous infusion via a peripheral line.

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

7.2.3 *Drug Availability*: Mesna is commercially available in 4 and 10 ml ampules containing 100 mg/ml.

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

7.2.5 *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.

7.3 Doxorubicin *(Adriamycin, Rubex)*

7.3.1 *Dose Formulation*: Doxorubicin is available as a red powder for injection in 10, 20, 50, 100 and 150 mg vials. Five, 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.

7.3.2 *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.

7.3.3 *Drug Availability*: Doxorubicin is commercially available.

7.3.4 *Storage*: Adriamycin RDF or Rubex intact vials are stable 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 as stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

7.3.5 *Side Effects*:

1. Hematologic: Leukopenia *(dose-limiting)*, also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.
2. Dermatologic: Alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.
3. Gastrointestinal: Nausea and vomiting sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule.
4. Cardiovascular: Arrythmias, 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.
5. Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity.
6. Local effects: Vesicant if extravasated; flush along vein, facial flush.

7.4 Ifosfamide *(Ifex)*

7.4.1 *Dose Formation*: 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.

7.4.2 *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 *Drug Availability*: Ifosfamide is commercially available.

7.4.4 *Storage*: The intact, unreconstituted vials are stored at room temperature. The sterile reconstituted solution is stable for 1 week at 30-C or 3 weeks at 5-C. Ifosfamide liquifies at temperatures above 35-C.

7.4.5 *Side Effects*:

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

7.5 Dacarbazine *(DTIC)*

7.5.1 *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 nl 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 or normal saline. DTIC should be given as a continuous intravenous infusion via a central line.

7.5.2 *Mechanism of Action*: DTIC is classified as an alkylating agent. Activity may be the result of a 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.

7.5.3 *Drug Availability* : DTIC is commercially available. If there is any difficulty in obtaining DTIC for protocol use, please contact June Brouillette at Bayer Corporation *(203/812-2355)*.

7.5.4 *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 D5W or NS, it is stable for 24 hours if refrigerated, and 8 hours at room temperature and protected from light.

Photodegradation: The manufacturer of dacarbazine states that the drug dose not decompose when left at room temperature under normal lighting conditions for eight hours.

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

7.5.5 *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.

7.5.6 *Side Effects*:

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

7.6 Filgrastim *(r-metHuG-CSF, Neupogen)* (4/28/97, 9/8/98)

7.6.1 *Dose Formulation*: G-CSF is available in preservative-free vials containing either 600 mcg of G-CSF in 2 ml buffered sterile solution or 480 mcg in 1.6 ml of solution. Each 1 ml contains 300 mcg of G-CSF, a preservative-free solution containing 0.59 mcg acetate, 50 mg sorbitol, 0.004% Tween 80, 0.035 mg sodium, and 1 ml water for injection, USP pH 4.0.

G-CSF will be administered subcutaneously. Injection sites should be rotated. If the volume to be injected is > 1.5 ml, the dose should be divided in half and both doses should be given at the same time in two sites. Patients will be instructed in self-administration. Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

7.6.2 *Mechanism of Action*: Filgrastim is a human granulocyte colony-stimulating factor *(G-CSF)* produced by recombinant DNA technology. G-CSF regulates the production of neutrophils with the bone marrow. Endogenous G-CSF is a glycoprotein produced by monocytes, fibroblasts and endothelial cells. r-met HuG-CSF is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by Escherichia Coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. Phase III clinical trials have demonstrated that G-CSF significantly reduces the incidence of febrile neutropenic episodes. With discontinuation of therapy, neutrophil counts returned to baseline, in most cases within 4 days.

7.6.3 *Drug Availability*: G-CSF is available from Amgen, Inc. **(9/8/98)**

7.6.3.1 G-CSF is being supplied free-of charge for this study by Amgen, Inc. and is available through Oncology Therapeutics Network *(OTN). Filgrastim orders from U.S. sites only will be accepted.*

To obtain a supply of G-CSF, complete the Filgrastim *(G-CSF)* Drug Request Form supplied in Appendix VI and fax to: Oncology Therapeutics Network, *Clinical Shipments Fax*: *(650)* 952-1588; this number should be used for clinical shipping requests. General Phone: *(800)* 370-2508

Orders will be shipped *(refrigerated)* Monday through Thursday for next day delivery. The initial shipment will be delivered by 10:30 a.m, subsequent shipments will be delivered by 3:30 p.m. Orders

received on Friday will be shipped the following Monday, unless the institution specifically requests Saturday delivery on the Drug Request Form and can guarantee accepting the delivery. Emergency shipments will be made on the same day with next day delivery when the drug request is received by 12 noon PT by OTN.

7.6.3.2 Reorders will be sent directly to OTN, ATT: Clinical Shipments, fax *(650)* 952-1588. The contact person is Fadia Alaraj, telephone *(800)* 370-2508.

7.6.3.3 For this study, G-CSF is supplied in 480 mcg/1.6 ml vials. Initial order quantities will be 100 vials/patient; reorder quantities will be in 10 vial increments. Unused drug at the site upon termination of the study will be returned to OTN with a completed Return Medication Packing Slip *(Appendix VII)* included identifying for which study the drug was originally shipped.

7.6.4 *Storage*: Unopened vials should be stored in a refrigerator at 2-8°C *(36-46°-F)*. Avoid shaking. Do not freeze. If accidentally frozen for a short while *(< 24 hours)*, it may still be used.

Prior to injection, G-CSF 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. G-CSF is stable for at least 1 year when stored at 2-8°C.

7.6.5 *Side Effects*:

Musculoskeletal: Mild to moderate medullary bone pain in 20% to 25% of patients.

Dermatologic and Hypersensitivity: Redness, swelling, itching, and pain may occur at the injection site. Transient, generalized rash has been reported occasionally. Anaphylactoid and allergic reactions have been reported rarely.

Hematologic : Leukocytosis occurs occasionally.

Other: Less frequently reported side effects include transient supraventricular arrhythmia, splenomegaly, and vasculitis. Transient increases in serum concentrations of uric acid. LDH, alkaline phosphatase and leukocyte alkaline phosphatase have been reported after cytotoxic chemotherapy.

7.7 Drug Dose Modification

The doses of chemotherapy will be attenuated as noted below. The most severe toxicity should determine the degree of attenuation.

7.7.1 *Hematology Toxicity*

7.7.1.1 Ifosfamide, Doxorubicin and DTIC doses are to be modified based both on the nadir *(day 14)* counts of the previous cycle and counts obtained on 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 Dr. Ettinger.

Absolute Neutrophil Count *(Reduce doses only if ANC is <1000 for > 5 days)*

ANC Nadir of Last Course	*ANC Day 1 of Each Cycle* ≤ 1500	*% Dose to Give* > 1500
> 1000	0 %	100%
500-1000	0 %	80%
< 500	0 %	70%

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.

Platelets Nadir of Last Course	*Platelets Day 1 of Each Cycle* ≤ 100,000	*% Dose to Give* > 100,000
> 75, 000	0 %	100%
50,000-75,000	0 %	80%
< 50,000	0 %	70%

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 Day 1 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 based on the previous course's nadir counts. However, if the counts have not recovered in two weeks, the Study Coordinator should be contacted. 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 for treatment as outlined. The treatment schedule will then proceed in the usual sequence.

7.7.2 *Gastrointestinal Toxicity (Ifosfamide, Doxorubicin, DTIC)*

Nausea and/or vomiting should be controlled with adequate antiemetics. If Grade III nausea/vomiting occurs in spite of antiemetics, the dose should be reduced by 25% for the next course. If tolerated, increase back to 100% dose as soon as possible.

If on Day 1 of any treatment cycle the patient has mucositis, the treatment should be withheld until the mucositis is cleared. If acute Grade III mucositis occurs at any time, the dose should be given at 75% dose when the mucositis is completely cleared.

7.7.3 *Hepatic Toxicity*: give the following percent of previous course's dose based on the patient's bilirubin the day of treatment.

Bilirubin *(mg/dl)*	Doxorubicin	Ifosfamide	DTIC
≤ 1.5	100%	100%	100%
>1.5 - ≤ 3.0	50%	100%	100%
>3.0 - ≤ 5.0	25%	75%	100%
5.0	0	0	100%

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

7.7.4.1 Mild Somnolence (sleeping constantly but easily aroused and oriented): Decrease dose of narcotics or antiemetics; continue ifosfamide with no change in dose.

7.7.4.2 Moderate Somnolence *(difficult to arouse or disoriented when finally awakened)*; discontinue IFOS until toxicity clears and then reinstitute at same dose. If moderate somnolence recurs, again discontinue IFOS and reinstitute at a 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.

7.7.4.3 Visual Hallucinations, Confusion, Catatonia: Hold IFOS, reinstitute at 25% reduced dose with next course minimizing any other psychoactive medications. If symptoms recur, decrease IFOS dose by another 25% with the subsequent course. If symptoms recur after a 50% dose reduction, discontinue permanently.

7.7.5 *Cardiac Toxicity*

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.

7.7.6 *Genitourinary*

Cystitis: IFOS-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 IFOS. Reinstitute IFOS at a 50% reduced dose when hematuria has cleared. If Grade 2-3 bladder toxicity occurs at the 50% dose reduction, discontinue IFOS permanently. IFOS may be escalated to full dose after dose reduction with subsequent courses if no hematuria occurs at the 50% dose reduction.

7.7.6.1 Nephrotoxicity: Give the following percent of the previous course's dose for nephrotoxicity based on renal function on the day of treatment:

Serum Creatinine	Doxorubicin	DTIC	Ifosfamide
<1.5 mg/dl	100%	100%	100%
1.5-2.0 mg/dl	100%	100%	75%

2.1-3.0 mg/dl	100%	100%	50%
>3.0 mg/dl	100%	100%	0%

7.7.7 *Miscellaneous Toxicity*

7.7.7.1 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)*.

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

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

7.7.7.4 Alopecia: IFOS and Doxorubicin cause total alopecia.

7.7.7.5 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.

7.8 Disease Progression

Patients who show progressive disease at the primary site during the preoperative period, will not receive post-operative chemotherapy. If progressive disease is noted after any preoperative 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 the study. They may be treated with other forms of palliative chemotherapy.

7.9 RTOG/Adverse Drug Reaction Reporting

7.9.1 The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

7.9.1.1 Any ADR which is both serious *(life threatening, fatal)* and unexpected.

7.9.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.9.1.3 Any death on study if clearly related to the commercial agent*(s)*.

7.9.1.4 Acute myeloid leukemia *(AML)*. The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.9.2 The ADR report should be documented on the FDA form 3500 *(Appendix V)* and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
(301) 230-2330
Telephone available 24 hours
fax # 301/230-0159

7.10 ECOG/Adverse Drug Reaction Reporting

7.10.1 All toxicities should be coded according to the RTOG Common Toxicity Criteria and the RTOG Acute Radiation Morbidity Scoring Criteria *(Appendix IV)*.

ECOG suggests ADRs to be reported on the Adverse Reaction *(ADR)* Form for Investigational Drugs *(#391RF)*. The form must be signed by the treating investigator. However, the MedWatch *(FDA Form #3500)* is also acceptable for reporting ADRs on commercial arms. All ADR reports must be accompanied by copies of supporting documentation. In addition, your institution's Investigational Review Board must be notified.

7.10.2 This protocol contains COMMERCIAL AGENTS only: Mesna, Doxorubicin, Ifosfamide, Dacarbazine *(DTIC)*, and G-CSF. Events indicated below must be reported in the manner specified.

For:

- Any death while on treatment if clearly related to commercial agent
- Any ADR which is BOTH serious *(life threatening [grade 4] or fatal [grade 5])* AND unexpected
- Any increased incidence of a known ADR
- Occurrences of second malignancies *(include protocol reference number, time from diagnosis to development of second malignancy and any characterization of the second malignancy, such as AML-FAB sub-type, cytogenetics, etc.)*

7.10.3 Call the ECOG Coordinating Center within 24 hours of the event. Submit original written ADR form to the ECOG Coordinating Center within 5 working days of the event. In addition, a copy must be mailed to the Investigational Drug Branch *(IDB)* within 10 days and your institutional Review Board *(IRB)* must be

notified.

The ECOG Coordinating Center will call the RTOG office to report ADR telephone calls and will forward ADR reports to RTOG.

	NCI/CTEP Secondary AML/MDS Report Form[1]	ECOG Second Primary Form[2] *(Form #630)*
AML/MDS	X	
All other secondary cancers		X

1 To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and to the NCI, accompanied by copies of the pathology report and when available, a copy of the cytogenetic report.

2 To be submitted to ECOG within 30 days of diagnosis of a new primary cancer during or after protocol treatment, regardless of relationship to protocol treatment. Not for use for reporting recurrence or metastatic disease. A copy of pathology report should be sent, if available.

NCI Telephone Number: ***(301)*** **230-2330**
NCI FAX Number: ***(301)*** **230-0159**
NCI Mailing Address:
IDB
P.O. Box 30012
Bethesda, MD 20824

ECOG Telephone Number: ***(617)*** **632-3610**
ECOG Mailing Address
ECOG Coordinating Center
Frontier Science
ATTN: ADR
303 Boylston Street
Brookline, MA 02146-7648

7.10.4 *Non-Treatment Related Toxicities*: If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the data forms which are to be submitted to the ECOG Coordinating Center according to the Data Submission Schedule. This does not in any way obviate the need for reporting the toxicities described above.

8.0 SURGERY

8.1 Biopsy may be by incisional biopsy or core needle biopsy. Sufficient tumor must be obtained to determine the diagnosis of 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 needle biopsy is done, care must be taken to tatto or otherwise identify the biopsy site so that it may be excised at the time of resection.

8.2 Resection of the sarcoma will occur following combined preoperative radiation and chemotherapy. The resection should be done with a goal to have negative margins. Quality assurance for surgical resection will be provided by assessment of the specimen by surgical pathology *(see Section 10.0)*. Absence of tumor on ink will be accepted as a negative margin.

8.3 The surgeon and radiation oncologist will consult after diagnosis and prior to the institution of neoadjuvant therapy. Plans for neoadjuvant therapy and subsequent surgery can be made. Following neoadjuvant therapy the surgeon, radiation therapist and medical oncologist see the patient again. Definitive plans for resection are made at this time. If deemed necessary, plastic surgery may be consulted at this time.

8.4 Definitions of operative procedures will be made following pathologic evaluation of the resected specimen *(no more than two weeks post operation*). The definitions include:

8.4.1 *Amputation (For type of resection see 8.4.2.1 - 8.4.2.4. This applies to amputations as well).*

8.4.2 *Non-amputation and the margins achieved* **(4/28/97)**

8.4.2.1 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.

8.4.2.2 Marginal Resection - All gross disease removed; less than compartmental or muscle group excisions; microscopically positive margins. These patients will receive postoperative radiation and continue on protocol *(see Section 6.3)*.

8.4.2.3 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.

8.4.2.4 Radical Excision - Entire anatomic compartment and negative microscopic margin.

8.4.2.5 Periosteum - If periosteum is resected in extremity sarcomas, consideration should be given for internal fixation.

8.5 Definitive Surgical Procedure.

The surgical treatment necessary to resect the tumor with negative margins should be used. These definitions noted above will be recorded in the surgical form.

8.6 Principles of Surgery

8.6.1 All lesions of the trunk and extremities will be treated with conservative resection *(minimal wide excision)* and neoadjuvant chemoradiation. 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 done from the closest margin and must be confirmed as being free of tumor. If postoperative pathology evaluation reveals positive soft tissue margins other than bone, nerve or large blood vessels, this margin should be resected if possible. If bone, major blood vessel or nerve is microspocially positive, additional radiation should be given as noted in the protocol. In general, lymph node dissection is not recommended but a sampling can be performed if regional lymph nodes are clinically enlarged or if the primary tumor is over a major node station. Elective node sampling may be performed in patients with epitheloid sarcoma, or clinically positive lymph nodes. Primary tumors overlying major lymph node stations may best be treated with surgical resection including node dissection. Marker clips *(titanium)* should be placed to help guide the radiation oncologist. Closed wound suction drainage should be used in all anatomic regions *(Davol, Hemavac, etc.)*. The drains should exit the skin close to the edge of the surgical incision. External compression for extremity resections with ace wraps or compression dressings is advised.

8.6.2 State *clearly* in the operative note what type of surgical procedure was performed, and from where the frozen section of the margins was taken.

8.6.3 Because all patients will have had neoadjuvant radiation and chemotherapy and radiation, special care must be given to skin flaps. Use of muscle flaps, pedicled myocutaneous flaps, and even free flaps is encouraged to fill dead space and used if there is any concern about the viability of the wound flaps.

8.6.4 In general, the following principles should be followed in postoperative management of these patients:
Maintain staples for one month.
Bedrest for 10-14 days for lower extremity lesions.
Leave drains until drainage is < 15 cc/day.
Begin rehabilitation slowly.

8.6.5 Resectability will depend upon the judgment of the operating surgeon. For the extremities, resection must be limb salvage procedure. For other anatomic area it must be judgment of the operating surgeon that he/she may reasonably expect to obtain negative margins. Extremity patients who are not resectable without amputation, may be amputated. Unresectable tumors elsewhere may be palliated with additional chemotherapy or radiation therapy.

8.7 Protocol Compliance *(See also Section 11.2.2)*

8.7.1 *Per Protocol* - Surgery completed by day 80 after start of treatment

8.7.2 *Minor Variation* - Surgery completed > day 80-day 94 after start of treatment

8.7.3 *Major Deviation* - Surgery completed ≥ day 95 after treatment start.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY (4/28/97)

10.1 Assessment of Pre-treatment Biopsy Specimen

10.1.1 *Central Pathology Review*

a) Recuts of all histology slides, a representative paraffin tissue block and a copy of the surgical pathology report must be mailed with a Pathology Submission Form to:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143

b) Immunohistochemistry slides should be made available upon request. A small sample should be snap-frozen and saved in tissue bank *(see Section 10.4)*. A small sample should be also fixed in glutaraldehyde for possible electron microscopy and should be sent upon request.

c) For ECOG institutions: Recuts of all histology slides and a copy of the surgical report must be mailed to the ECOG Pathology Coordinating Office *(PCO)*. If ECOG institutions submit paraffin

blocks, they will be returned to the contributing institution and slides will be requested. ECOG members will send pathology material to the ECOG PCO:

ECOG Pathology Coordinating Office
Evanston Hospital
Room B624
2650 Ridge Avenue
Evanston, IL 60201-1797

Note: A copy of the completed ECOG Pathology Material Submission Form No. 638 will be sent to the ECOG Study Chair and to the ECOG Coordinating Center by the PCO. The ECOG PCO will log the materials and route them to LDS Hospital.

10.1.2 *Type of Specimen*

a) Needle core biopsy
b) Incisional biopsy
c) Excisional biopsy *(must include assessment of surgical margins: positive, close, negative)*
d) Fine needle aspiration not acceptable for accurate grading and phenotyping

10.1.3 *Histopathologic Assessment*

a) Sarcoma phenotype as categorized by the WHO *(1994)*[29]
b) Histologic grade *(grade 2 or 3)*. Grading of soft tissue sarcomas is an imperfect endeavor, not without limitations and pitfalls. This stems from the markedly different histologies between different sarcoma types. All tumors in this study must be at least intermediate grade *(2 or 3)*. Grades 2 and 3 tumors may be separated by features such as mitotic rate *(usually > 6 mitotic figures per 10 HPF)*, percent necrosis, cellularity, pleomorphism, and differentiation. Mitotic rate and necrosis appear to be the most important prognostic factors, and should be useful for separating grade 2 from 3.[30] Costa et al.[31] recommend separating grades 2 and 3 based upon presence or absence of necrosis. Another 3 scale system by Trojani and et al.[32] employs degree of tumor differentiation, mitotic activity, and tumor necrosis; each assigned a quantitative value, with the sum of these three values used to determine grade. A three-scale system would provide two separate groups in our study, as only high and intermediate grade sarcomas will be evaluated. The 3 scale grading system is widely used and should be readily adaptable to this study.
c) Mitotic rate *(> 6 per HPF)*:Yes/No
d) Necrosis *(0, < 50%, or ≥ 50%)*
e) Tumor matrix *(sparse, myxoid, fibrous, etc.)*
f) Vascular space invasion *(Yes/No)*
g) Host lymphoplasmacytic response *(+/-)*
h) Margin of infiltration *(pushing, infiltrative, not evaluable)*

10.2 Assessment of Resected Tumor

10.2.1 *Central Pathology Review*

a) Recuts of all histology slides, the surgical pathology report, and a representative paraffin block and a Pathology Submission Form should be submitted to LDS Hospital per Section 10.1.1.

10.2.2 *Gross Parameters of Tumor*

a) Tumor size *(cm greatest dimension).*
b) Description of margins including cm or mm to closest margin.
c) Gross photograph of tumor desireable.

10.2.3 *Handling of Gross Specimen*

a) External surface specimen should be painted with india ink prior to sectioning.
b) Tumor should be thoroughly sampled *(at least 1 section per 1 cm of greatest tumor dimension)*.

10.2.4 Histopathologic Assessment[33]

a) Percent of viable neoplasm *(0, < 25%, 25-50%, > 50-75%, > 75%)*
b) Percent necrosis *(0, < 50%, > 50%)*
c) Degree of fibrosis/hyalinization *(0, < 50%, ≥ 50%)*
d) Tumor margin *(pushing, infiltrative)*
e) Host lymphoplasmacytic response *(+/-)*
f) Vascular space invasion *(Yes/No)*
g) Surgical resection margin *(+, close, wide)*
h) Degree of intratumoral hemorrhage *(0, < 50%, ≥ 50%)*

10.3 Ancillary Studies

10.3.1 Additional biologic studies will be performed on the paraffin sections including immunohistochemistry for p53 protein, multi-drug resistance protein *(p-glycoprotein)*, and proliferation marker *(e.g. Ki-67)*. DNA content may be determined by image analysis.

10.4 Frozen Tissue Bank

10.4.1 Many informative biological studies can be done with snap-frozen tissue samples. These include molecular biologic studies of oncogenes and tumor suppressor genes, including frozen-section immunohistochemistry *(e.g. for MDM2 protein)*, polymerase chain reaction and DNA sequencing techniques. Frozen tissue may also be put in tissue culture or used in flow cytometry for determination of DNA content. Many additional studies will be possible. Details and methods will be determined as the study progresses.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Study Parameters and Time Done	On Entry to Study	Every Week During RT	Prior to Each MAID Cycle	Every Week During MAID	Prior to Surgery	Post RX 6 Weeks	F/U 2 Years Post Therapy Every 3 Months	F/U Every 6 Months Years 2-5	F/U >5 Years Post Therapy Yearly
History and PE	X	X	X		X	X	X	X	X
Hgt *(cm)*	X								
Wgt *(kg)*	X	X	X		X	X	X	X	X
Body Surface *(m^2)*	X								
KPS	X		X		X	X	X	X	X
Biopsy *(core needle or incisional)*	X								
CT of Chest	X		X[c]		X	X		X[e]	X
MRI or CT of Primary Tumor[a]	X				X	X		X[e]	X
MUGA or Echocardiography for Ejection Fraction[b]	X				X			As Indicated	As Indicated
Chest X-ray	X		X[c]		X		X		X
Hct, Hgb, WBC	X	X[f]	X	X	X	X	X	X	X
Differential	X	X[f]	X	X	X	X	X	X	X
Platelet Count	X	X	X	X	X	X	X	X	X
Creatinine, SGOT	X		X		X	X	X	X	X
Alkaline Phosphatase	X		X		X	X	X	X	X
Bilirubin	X		X		X	X	X	X	X
Urinalysis	X		X			X	X	X	X
Pregnancy Test	X[d]								

a. MRI should be done in all extremity sarcomas, though CT will be accepted. CT should be done in sarcomas of the torso wall. See Section 11.9 for MRI guidelines.
b. Patients with history of myocardial infarction *(MI)* may participate in study if they are greater than 6 months post MI and have radiologic evidence of an ejection fraction of ≥ 50%. Ejection fraction may be assessed with MUGA scan or echocardiography.
c. Repeat if clinically indicated.
d. To be performed in all females with child bearing potential.
e. Do every 6 mos following treatment.
f. Twice weekly during G-CSF administration.

11.2 Response Assessment

11.2.1 *Measurement of Response*

Response to preoperative chemotherapy and radiation will be measured by comparing tumor size at time of registration for the protocol with measurements taken 0 to two 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).

- Complete response ***(CR)*** - Disappearance of all measurable tumor as measured by MRI, CT or physical examination ***(PE)***. This is the order of preference of items for measurement.
- Partial response ***(PR)*** - 50% or greater decrease in product of perpendicular dimensions as measured on MRI, CT or PE. This is the order of preference of items for measument.
- Minor response ***(MR)*** - A measurable decrease of the product of perpendicular dimensions as measured on MRI, CT or PE of 25% - 50%. This is the order of preference of items for measurement.
- Stable disease ***(SD)*** - Stable disease is defined as a < 25% decrease in size or < 25% increase in size of the measured lesion.
- Progression ***(P)*** - Progression is defined as an increase in size of the lesion by >25% as defined by the product of the perpendicular dimensions on MRI, CT or PE. This is the order of preference of items for measurement.

11.2.2 *Record of Timing of Therapies*

Modification of chemotherapy dose associated with toxicity is noted in Section 7.7. Delays in institution of chemotherapy, radiation therapy *(RT)* or surgery should be recorded. We anticipate 21 days between cycles of chemotherapy. Ideally there will be 2 days between the completion of chemotherapy and the institution of the preoperative radiation doses in the treatment arm. Surgery should be completed by day 80 of protocol *(time from first chemotherapy to time of surgery)*. Delay from day 80 to 94 will be considered a minor variation. Delay beyond day 94 will be considered a major deviation. Chemotherapy should be instituted between 21 days and 35 days following surgery. Delay beyond 35 days following surgery will be considered a major deviation.

11.3 Wound Complications

Wound complications are to be reported. They will be categorized as noted below. These categories will also apply to the control or preoperative radiation therapy arm of the protocol.

11.3.1 *Category 1*: This is a minor wound complication such a minor skin separation or delayed drain removal. This category of complication does not result in delayed institution of post operative chemotherapy *(see Section 11.2.2)*.

11.3.2 *Category 2*: This represents a more serious problem which seriously delays the institution of adjuvant chemotherapy. Included would be a major infection, but a complication in which limb loss is not threatened.

11.3.3 *Category 3*. This represents a very serious infection or vascular complication in which limb loss, major soft tissue loss or skin loss is threatened.

11.5 Definition of Recurrence

Recurrence represents the time when recurrent or persistent disease is noted. This must be biopsy proven.

11.6 Time to Recurrence

Time to recurrence represents the time from registration to time that recurrence is biopsied.

11.7 Survival

Survival represents the time from registration to the time of death.

11.8 Follow-up

Patients will be followed until death. Followup must include MRI or CT scans as indicated. Every effort should be made to obtain an autopsy to document the extent of disease at the time of death.

11.9 Guidelines for MR Imaging Protocol for Musculoskeletal Sarcomas

11.9.1 Musculoskeletal sarcomas are imaged using standard spin echo *(SE)* sequences in planes designed to demonstrate both the compartmental and longitudinal extent of the lesion. The number of slices, slice thickness, image gap, image matrix and field-of-view will vary depending on the size and location of the lesion and cannot be specifically defined in the protocol. In each case, the primary determinant of the slice thickness and matrix/field-of-view combination is the requirement that the entire tumor be imaged with sufficient surrounding tissue to include compartmental margins, adjacent joints and draining nodal groups. Sufficient resolution must be maintained to define the relationship of the tumor to vessels and nerves passing nearby. Similarly, the number of slices and slice gap will vary with larger tumors requiring more slices and, occasionally, slice gapping to fully evaluate the tumor. Rapid acquisition gradient echo and turbo spin echo sequences may be substituted for standard spin echo sequences when they are available, provided that identical sequences are used prior to and following contrast injection.

11.9.2 Intravenous Gd-DTPA is administered at 0.1 mmol/kg body weight. Both the pre-and post-

contrast T1 weighted sequences are multi-slice sequences covering the entire tumor. Image sequences are obtained immediately following infusion and at 1, 3, 5 and 10 minutes following the infusion. The post infusion images are reviewed and the regions of greatest enhancement identified. The signal value in this

area is measured on each sequence and compared with subcutaneous fat *(which should not enhance)* in an area away from the tumor. The ratio of fat to tumor is them plotted relative to time from injection.

11.9.3 *Suggested standard sequences*:

Plane	Sequence	TR	TE
Pre Contrast:			
Axial	T1 SE	500-7000	10-15
Axial	T2 SE	2200-2500	20-30 & 80-90
Longitudional	T2 SE	2200-2500	20-30 & 80-90
Post Contrast:			
Axial	T1 SE	500-700	10-15

12.0 DATA COLLECTION

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

12.1 Summary of Data Submission (4/28/97, 9/8/98)

Item	Due
Demographic Form **(A5)**	Within 1 week of study entry
Initial Evaluation Form **(I1)** Diagnostic Pathology Report **(P1)** Pathology Slides/Blocks **(P2)**	Within 2 weeks of study entry
Radiotherapy Form **(T1)**	At completion of induction RT
Dosimetry Information: Films *(simulation and portal)* **(TP)** Calculations **(TL)** Daily Treatment Record **(T5)** Isodose Distribution **(T6)** Boost Films *(simulation and portal)* **(T8)**	At completion of all RT
Chemotherapy Flowsheets **(M1)**	Within 6 weeks of start of pre-op and post-op chemotherapy; within 2 weeks after completion of pre-op and post-op chemotherapy
Surgery Form **(S1)** Operative Notes **(S2)** Surgical Pathology Report **(S5)** Pathology Slides/Blocks **(P2)**	Within two weeks of surgery
Post-Induction Evaluation Form **(F0)**	At time of re-evaluation
Radiotherapy Form **(TF)**	Within one week of end of post surgical RT if given
Follow-up Form **(F1)**	At 6, 9, and 12 months from treatment start; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/relapse and at death
Autopsy Report **(D3)**	As applicable

12.2 Dosimetry Submission

12.2.1 Dosimetry data must include complete and final information for patients receiving post operative RT. These include completed T5, T6 as well as T8 *(boost films)*. Patients who do not receive post operative RT, do not require T8 films. All dosimetry data will be submitted directly to RTOG, including ECOG

members.

12.3 ECOG Data Submission

12.3.1 ***Note:*** ECOG institutions should send all radiation oncology material directly to RTOG.

12.3.2 *For ECOG institutions* - originals of completed forms must be sent by the institutions to the:

ECOG Coordinating Center
Frontier Science
ATTN: Data
303 Boylston Street
Brookline, MA 02146-7648

The RTOG case number as well as the ECOG case number should appear on every form. Investigators should retain a copy of their records. The ECOG Coordinating Center will forward the date-stamped originals to RTOG Headquarters. ECOG members should send forms directly to RTOG. RTOG forms should be used. **DO NOT use ECOG data forms except for the ECOG Pathology Material Submission Form NO. 638, the ECOG Second Primary Cancer Form No. 630 and the Adverse Reaction *(ADR)* Form for Investigational Agents 391RF.**

12.3.3 ECOG will attach a forms appendix to their members' version. It will be the responsibility of the institutions to copy the attached forms and to maintain a supply of available forms for data submission.

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

The following are the study endpoints. They will be analyzed in detail at the completion of this study.

13.1.1 *Initial Response to the Preoperative Chemoradiation*

Both the clinical and the histopathologic responses will be assessed. See Sections 10.2.4 and 11.2.1 for details.

13.1.2 *Local Recurrence and Distant Metastasis*

The local recurrence rate and the distant metastasis rate within two years of surgery will be reported.

13.1.3 *Toxicity*

Both acute and late toxicity within the first two years after registration will be summarized.

13.1.4 *Wound Complications*

Wound complications will be divided into three categories as listed in Section 11.3.

13.1.4 *Treatment Delivery*

The treatment delivery will be divided into three phases: preoperative, surgical and postoperative. The number of patients who completed each phase per protocol will be reported. Both dose and timing variations will be recorded.

13.1.5 *Survival*

Absolute survival as well as local and distant disease-free survival will be studied, but by the time of the initial treatment paper most patients will still be alive.

13.2 Patient Accrual and Study Duration

This is an intergroup study. From a survey of RTOG member institutions, **we project that 30 patients can be accrued in about one year.** All the ratios, such as the initial response rates, local recurrence rates and wound complications rates, can be estimated with a standard deviation of no more than 0.09. All patients will be followed until death as is usually done in RTOG, but the initial treatment paper will be prepared after the last patient has been followed for two years.

13.3 Semi-Annual Reports

Semi-annual reports will be prepared and published in the RTOG Meeting Reports until the initial treatment paper is submitted to a peer-reviewed journal. In general, these reports will contain information about the patient accrual rate, data quality, compliance rate of treatment delivery, distribution of important prognostic baseline variables and the frequencies and severity of the toxicities.

13.4 Inclusion of Women and Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the possible difference in any of the above endpoints between men and women, or whites and non-whites, will be investigated.

13.5 Revised Accrual and Study Duration (9/8/98)

This is an intergroup study. The RTOG Research Strategy Committee reviewed and approved the proposal to increase the sample size from 30 to 60 patients in order to obtain more precise estimates of the standard error *(0.065)* associated with the initial response rates, local recurrence rates, and wound complications rates, and to guard against a rate up to 10% for inevaluable cases due to retrospective ineligibility and incomplete data submission. From the accrual rate of the last six months, **the accrual of the additional 30 patients is expected** to be completed within 15 months. All patients will be followed until death as is usually done in RTOG, but the initial treatment paper will be prepared after the last

patient has been followed for two years.

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APPENDIX I

RTOG 95-14
ECOG R9514

A PHASE II STUDY OF NEOADJUVANT CHEMOTHERAPY AND RADIATION THERAPY IN THE MANAGEMENT OF HIGH-RISK, HIGH-GRADE, SOFT TISSUE SARCOMAS OF THE EXTREMITIES AND BODY WALL

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits and alternatives. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

Combining radiation with surgery improves local tumor control in patients with soft tissue sarcomas. The primary purpose of this protocol is to test whether patients receiving chemotherapy, consisting of Mesna, Adriamycin, Dacarbazine and Ifosfamide with radiation therapy and surgery will have improved control of the tumor. In addition, my physicians hope to learn whether this therapy changes wound healing. Tumor tissue removal also must be studied to learn more about how these tumors grow and function.

DESCRIPTION OF PROCEDURES (4/28/97)

I will receive three cycles of chemotherapy *(one course every three weeks)* alternating with two courses of radiation therapy *(RT)*. Following the third cycle of chemotherapy, I will have the tumor removed surgically. There will be approximately 2-1/2 months between the start of the chemotherapy and surgery. The surgery will be planned to remove the complete tumor. If there are any tumor cells at the edges of the removed tissue, rather than normal tissue, I will have additional radiation. Regardless of whether I receive the additional radiation treatments, I will receive three more cycles of chemotherapy following surgery. The chemotherapy in this study will consist of mesna, adriamycin, ifosfamide and dacarbazine. The day after my first cycle ends, I will also receive G-CSF which should reduce the incidence of fever caused by low blood counts from the other chemotherapy drugs. G-CSF will be provided free of charge for this study by Amgen, Inc, and will continue until my blood counts improve.

Each cycle of chemotherapy is given over four days as an i.v. *(in my vein)*. I will be hospitalized for each cycle. Three days after my first and second cycles of chemotherapy ends, I will start radiation treatments. Radiation is given as an outpatient. The radiation treatments take a few minutes once a day Monday through Friday over three weeks. The following table shows the planned schedule:

TX	Cycle 1 Days	RT* Days	Cycle 2 Days	RT Days	Cycle 3 Days	Surg Day	Cycle 4 Days	Cycle 5 Days	Cycle 6 Days
Mesna	1-4		22-25		43-46		101-104	122-125	143-146
Adria	1-3		22-24		43-45		101-103	122-124	143-145
Ifos	1-3		22-24		43-45		101-103	122-124	143-145
Dacar	1-3		22-24		43-45		101-103	122-124	143-145
RT		7-20		28-41					
Surgery						80			

* 11 treatments in 13-15 days.

My evaluation at entry into the study will include blood tests, a chest x-ray, and other appropriate tests to evaluate my cancer, as well as my general well being. I will have tests during chemotherapy and radiation treatments to monitor how I am doing. I understand that as part of this protocol I will be followed at least every three months for two years, though it may be more frequent if necessary. Later in the study, I will be followed every 6 months. Beyond 5 years I will be followed yearly.

Also, at the time of my diagnosis by biopsy or later at surgery some of my tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers" *(tests which predict how a patient with tumors like mine responds to treatment)* can be identified.

RISKS AND DISCOMFORTS

The risks associated with this treatment will be those associated with the cancer and the treatments given. The treatments used in this program may cause all, some, or most of the side effects listed below. The occurrence of acute leukemia has been reported rarely in patients treated with several cancer drugs. In addition, there is always the risk of new uncommon or previously unknown side effects occurring. Specific risks and discomforts are listed below:

Chemotherapy

The usual side effect of the chemotherapy drugs are, loss of hair, nausea, and/or vomiting, loss of appetite and decreased blood counts that may increase the chance of infection or bleeding.

Mesna can leave a bad taste in my mouth, cause diarrhea, headache, nausea, and vomiting. Rarely, it causes low blood pressure, and allergic reactions.

Adriamycin may cause nausea, vomiting, mouth sores, hair loss, and discoloration of the nails, skin, and urine. Adriamycin can decrease blood counts which could lead to an increased risk of infection, weakness, or bleeding complications. I might need antibiotics, hospitalization, and/or transfusions if these problems are severe. If some of the drug accidently leaks out of the vein where it is injected, severe irritation and ulceration of the skin and soft tissues can occur. With prolonged usage, there is a risk of heart failure, which might be permanent. Symptoms of heart failure include shortness of breath, decreased exercise tolerance and swollen ankles.

Ifosfamide may cause nausea and vomiting, loss of appetite, constipation, diarrhea, blood in the urine, hair loss, confusion, or drowsiness. To prevent damage to the bladder, another drug called Mesna will be given. Ifosfamide can produce abnormalities of liver and kidney blood tests, which usually do not lead to significant health problems. It also can lower blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need antibiotics, hospitalization, and/or transfusions if these problems are severe.

Dacarbazine may cause "flu-like" symptoms of fever, chills and tiredness. Less commonly it can cause a metallic taste in the mouth, sensitivity to light, and hair loss. It can also produce discomfort at the site of injection. If the drug leaks out from my vein during administration, it can injure my skin and nearby tissues.

G-CSF is given by injection in the skin and there is some discomfort associated with this. It also may cause mild to moderate muscle/bone aching which is usually relieved with mild medication such as acetaminophen.

Radiation Therapy

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)*. In general, most radiation reactions *(other than fatigue)* are limited to the site being treated. For example, if my leg is being treated, I will not feel nauseated from radiation treatment. My doctor will specifically identify those risks connected with the location of my tumor.

Early reactions may consist of the following:

1) Skin reactions. This may be mild *(slight redness)* to severe *(painful skin blistering)*. Skin reactions may become most noticeable during chemotherapy courses. If the head and neck area is being treated, the lining of the mouth and throat may become sore and red, causing difficulty swallowing. These reactions will subside with time.
2) Fatigue *(tiredness)*. Many patients undergoing radiation complain of feeling tired.
3) Reduction in blood counts. Radiation can temporarily lower red blood cell, white cell and platelet counts,

possibly resulting in bleeding or infection.

4) If the abdominal wall is being treated, I may develop diarrhea.
5) Wound healing delay after surgery may result.

Late reactions may include:

1) Skin reactions. Skin in the treated volume may appear tanned and may stay this way for a number of years after radiation.
2) Fibrosis *(hardening of the tissues)*: Tissues in the treated area may feel hard and woody. If this occurs, it is likely to be permanent.
3) Pain in a limb. This symptom may occur one to several years after completion of treatment and may last for many years.
4) Swelling. This may occur in the first year after treatment. In many patients this will resolve. Some patients will have persistent swelling and will need to use elastic stockings. If severe, I may require the use of a pump that pushes swelling out of the extremity. Some patients will notice temporary swelling after strenuous activity.
5) Fracture. Radiation can make bones more susceptible to fracture.
6) Bruising. Irradiated skin, especially over the shin and elbow, may heal more slowly if injured or bruised.
7) If the abdominal wall is being treated, injury to the bowel is an uncommon but potentially serious side effect.
8) If the back area is being treated, injury to the spinal cord is a very rare but potentially serious complication.
9) Risk of cancer. Radiation can cause tumors in the irradiated tissues. Fortunately, this is rare *(1 in 2,000)* in adults but can occur many years after treatment.
10) Damage to other organs. If heart, lung, liver or stomach are in the field of treatment these organs could be damaged.

Surgery

Complications may occur when tumors are removed from the legs, arms, and body wall whether radiation or chemotherapy is given. While surgical treatment of these tumors result in wound healing delay or infection, the addition of radiation or radiation and chemotherapy may increase this problem. Ultimately, most patients will heal satisfactorily. Complications which may be associated with surgical procedures in this study will be described below.

Patients with tumors of arm or legs

1) Removal of large tumors from the arm or the leg may result in decreased function of that limb because of muscle, nerve or skin damage.
2) Uncommonly, 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. This is an uncommon occurrence.

Patients with tumors of the abdominal wall

1) Radiation and surgery or radiation, chemotherapy and surgery for tumors of the abdominal wall may result in failure of the wound to heal and occassionally the development of a hernia. 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 usually works well, it may result in wound infection and prolonged hospitalization.

Patients with tumors of the chest wall

1) 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, may require the use of plastic material. 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.
2) 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 the patient at increased risk for having heart or lung problems during surgery. Rarely, these complications may result in death.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that 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.

This study may be harmful to an unborn child. There is insufficient medical information to see whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. The results will be made available to the study participant prior to the initiation of this study. Pregnancy must be avoided during treatment. If I became pregnant I must notify my physician immediately.

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

CONTACT PERSONS

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

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include surgery performed off-study with or without radiation therapy or chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

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

VOLUNTARY PARTICIPATION

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

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG)* . If my hospital is an Eastern

Cooperative Oncology Group member, records of my progress will also be kept in a confidential file at their Headquarters. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration *(FDA)*, the National Cancer Institute *(NCI)*, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Patient Signature *(or Legal Representative)* Date

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

Code	SWOG	Karnofsky	ASCC
0	Fully active	90-100	H0
1	Ambulatory with symptoms	70-80	H1
2	No work but self-care	50-60	H2
3	Limited self-care, confined to be >50%	30-40	H3
4	Completely disabled	10-20	H4

New York Heart Association Functional Status	
Class I	No symptoms
Class II	Symptoms with moderate or severe activity
Class III	Symptoms with mild sedentary living
Class IV	Symptoms at rest

APPENDIX III - A

STAGING SYSTEM (AJCC, 4th edition - 1992)

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor 5 cm or less in greatest dimension

T2 Tumor more than 5 cm in greatest dimension

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph metastasis

Regional Lymph Nodes. The regional lymph nodes are those appropriate to the site of the primary tumor.

Unilateral Tumors

Head and neck	Ipsilateral preauricular, submandibular, cervical, and supraclavicular lymph nodes
Thorax	Ipsilateral axillary lymph nodes
Arm	Ipsilateral epitrochlear and axillary lymph nodes
Abdomen, loins and buttocks	Ipsilateral inguinal lymph nodes
Leg	Ipsilateral popliteal and inguinal lymph nodes
Anal margin and perianal skin	Ipsilateral inguinal lymph nodes

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Metastatic Sites. The lung is the most common site, but any body site may be involved.

STAGE GROUPING

Stage IA	G1	T1	N0	M0
Stage 1B	G1	T2	N0	M0
Stage IIA	G2	T1	N0	M0
Stage IIB	G2	T2	N0	M0
Stage IIIA	G3,4	T1	N0	M0
Stage IIIB	G3,4	T2	N0	M0
Stage IVA	Any G	Any T	N1	M0
Stage IVB	Any G	Any T	Any N	M1

HISTOPATHOLOGIC GRADE (G)

After the histologic type has been determined, the tumor should be graded according to the accepted criteria of malignancy, including cellularity, cellular pleomorphism, mitotic activity, and necrosis. The amount of intercellular substance, such as collagen or mucoid material, should be considered as favorable in assessing grade.

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

APPENDIX III - B

Enneking System for Staging of Sarcomas of Soft Tissues or Bone

Stage	Characteristic
I	Low Grade
IA	Intracompartmental
IB	Extracompartmental
II	High Grade
IIA	Intracompartmental
IIB	Extracompartmental
III	Any Grade
	N1 or M1

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

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

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

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

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

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

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

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

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

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

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

Investigational Agents

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

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

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(grade 4)* events which may be due to agent.	As above
- First occurrence of any toxicity *(regardless of grade)*.	Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.

	**A written report may be required.

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

- All fatal *(grade 5)* and life threatening *(grade 4)* known adverse reactions due to investigational agent.	Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within working days with a copy to IDB. *(Grade 4 myelosuppression not reported to IDB)*
- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.	Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.	**Report **in writing** to RTOG Headquarters and IDB within 10 working days.

****** See attached *(if applicable to this study)* NCI Adverse Drug Reaction Reporting Form

APPENDIX VI (9/8/98)

Filgrastim *(G-CSF)* Drug Request Form

(CoOp Protocol ID# RTOG 95-14), Amgen Protocol #950203, "Protocol Title: A Phase II Study of Neoadjuvant Chemotherapy and Radiation Therapy in the Management of High-Risk, High-Grade, Soft Tissue Sarcomas of the Extremities and Body Wall"

Requested by:

Pharmacist: _____

Institution: _____

RTOG Number: _____
(must be included)

Principal Investigator: _____

Phone #: _____

Ship To:

Name: _____

Address*: _____

_____

* Please do not use P.O. Box numbers

Fax: _____

		# of Vials*		Check One	
Pt. ID	Pt Initials *(Last, First)*	480 µg	RTOG Case#	Starter Supply *(For this pt.)*	Re-order *(For this pt.)*

*** Reminder: See protocol section on drug formulation for instructions regarding amounts of drug to order.**

G-CSF will be shipped *(refrigerated)* on Monday through Thursday for next day delivery.

Shipment will be made on the same date the drug requested is received.

G-CSF can also be shipped on Friday, **but only if the institution can guarantee** receipt of Saturday delivery.

Check here if requesting Saturday delivery.

_____
Date of Drug Request

_____
Pharmacist Signature

Return Completed, Signed, and Dated form to:

Oncology Therapeutics Network
Attn.: Drug Orders
Fax: 650-952-1588

APPENDIX VII (9/8/98)

RETURNED MEDICATION PACKING SLIP

Institution Name:_____

Address:_____

Principal Investigator:_____

Amgen Study No: 950203 Group Study No: RTOG 95-14

Study Title: A Phase II Study of Neoadjuvant Chemotherapy and Radiation Therapy in the Management of High-Risk, High-Grade, Soft Tissue Sarcomas of the Extremities and Body Wall

Instructions:
Per FDA requirements, please retain a copy of this completed form for your files. Drug being returned for any reason should be sent, together with this original form, to Oncology Therapeutics Network, 11698 San Marino Drive, Rancho Cucamonga, CA 91730. Only drug returns are to be sent to this address, no other correspondence. Questions may be directed to *(800)* 370-2508, Monday through Friday 8:00 am - 5:00 pm, Pacific Standard Time. Voice Mail is available at all other times.

Study in progress?

Yes No

Study completed per protocol?

Yes No

Reason drug returned? *(Please check one)*

Drug Expired

Unused drug being returned

Person Shipping Drug: _____
Drug being returned by:

Fed Ex UPS US Mail

Date: _____ No. of cartons: _____
Research Associate's/Pharmacist's Signature:

_____ Date: _____

Return receipt requested: Yes No

Fax number: _____

DESCRIPTION OF RETURN SHIPMENT

Drug Name & Vial Description _____ mcg/_____ml/vial	Lot Number	Number of Vials
Comments:		

TO BE COMPLETED BY AMGEN
Returned shipment received on _____ and checked by: _____
(Name)