

Combination of External Beam Radiotherapy with ^{153}Sm -EDTMP to Treat High Risk
Osteosarcoma and Patients with Solid Tumors Metastatic to Bone

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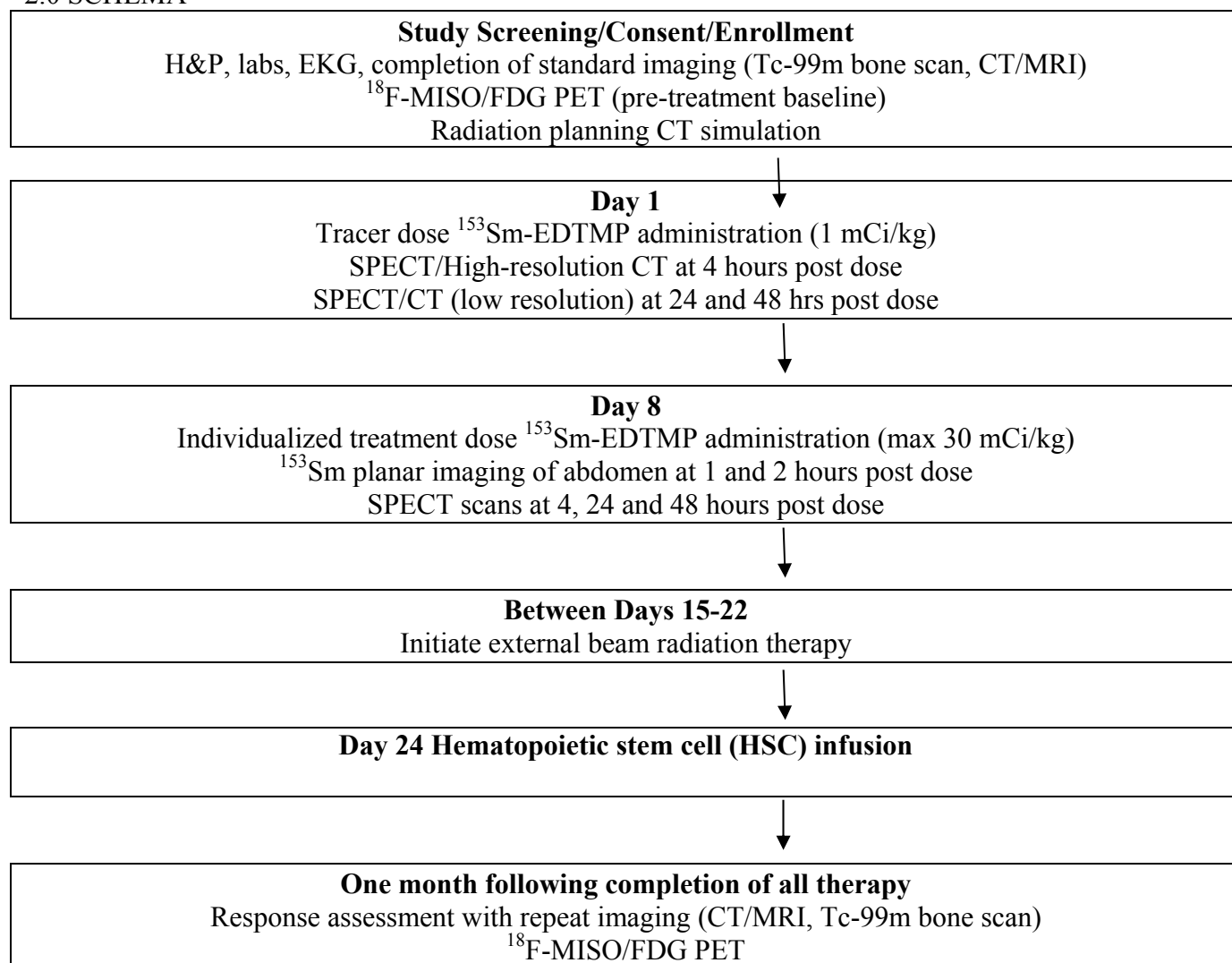
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2.0 SCHEMA



This study will have 2 strata: Stratum 1 is for patients with osteosarcoma. Stratum 2 is for patients with other high risk solid tumors metastatic to bone.

3.0 OBJECTIVES

3.1 PRIMARY OBJECTIVES

3.1.1 (Stratum 1 Only)

To assess the clinical response of high-risk osteogenic sarcoma to high-dose ^{153}Sm -EDTMP and external beam radiotherapy.

3.1.2 (Stratum 2 Only)

To estimate the response rate of diseases other than osteosarcoma to the combination of high-dose ^{153}Sm -EDTMP and external beam radiotherapy.

3.2 SECONDARY OBJECTIVES

3.2.1 To describe the toxicity and long-term effects of combined infusional ^{153}Sm -EDTMP and external beam radiation therapy.

3.2.2 To image tumors using [^{18}F]Fluoromisonidazole (^{18}F -MISO) PET scanning before and after treatment, and compare with clinical response as measured by radiographic imaging and/or histology.

3.2.3 To describe the distribution of absorbed doses delivered to each targeted lesion and the distribution of lesion equivalent uniform dose delivered to each patient.

3.2.4 To determine dosimetry measurements after initial tracer dosing, predict target total radiation exposure to tumor based on linear kinetics previously described, and calculate a subsequent combined treatment dose.

3.2.5 Stratum 1 Only

To observe overall survival and time to progression in patients treated with combined infusional ^{153}Sm -EDTMP and external beam radiation therapy, and model any relationship between total absorbed dose and progression.

4.0 INTRODUCTION

4.1 GENERAL BACKGROUND

Cure of osteogenic sarcoma relies on both definitive control of gross tumor masses and on effective treatment of micrometastatic disease. While systemic chemotherapy can be effective in the control of micrometastases, surgery is usually required to treat gross disease. Osteogenic sarcoma is relatively resistant to radiation therapy, limiting the utility of this treatment modality for local control. A mechanism to deliver radiation therapy at a high enough dose to be tumoricidal while sparing surrounding normal tissue would allow the incorporation of radiation

into the therapeutic armamentarium when up-front surgery is not feasible. In the event of good tumor shrinkage, this might allow for subsequent surgical intervention or other localized therapy such as cryoablation.

Studies of radiation therapy in osteogenic sarcoma were performed prior to 1980, and demonstrated that doses in the range of 66-80 Gy are required for a therapeutic response. Several studies point out that administration of less than 60 Gy is associated with only transient tumor control, and viable tumor has been found in amputation specimens even after treatment with 80 Gy or more (1-3). These doses are quite difficult to deliver using standard external beam radiation without exceeding the tolerance of surrounding normal tissue. Because of this, standard treatment regimens for osteogenic sarcoma do not incorporate radiation therapy. Even modern conformal techniques, such as intensity-modulated radiation therapy (IMRT) are of limited utility in the setting of multiple metastases, and are unable to treat micrometastatic disease. This is a hindrance to the cure of patients with multiple sites of metastatic disease or with unresectable tumors for which surgery will not provide complete control of gross disease.

Targeted radioisotope delivery has been pursued as an alternative to external beam radiotherapy for osteogenic sarcoma or to supplement external beam radiotherapy. One of the most promising agents being developed for this purpose is ^{153}Sm ethylenediaminetetramethylene phosphonic acid (^{153}Sm -EDTMP). This compound localizes to sites of new bone formation similar to technetium-99m methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) bone scintigraphy. The EDTMP moiety is structurally related to the chelating agent methylene diphosphonate that is complexed to technetium-99 for conventional bone imaging. This allows the delivery of radiotherapy to osseous metastatic lesions visible on conventional bone scan (4). A medium energy photon given off by the ^{153}Sm -EDTMP allows for standard scintigraphic scanning to monitor the delivery of radiation to the tumor.

Other characteristics of ^{153}Sm that make it of interest in the treatment of osteogenic sarcoma are the emission of tumoricidal beta radiation and a relatively short half-life. The tumoricidal beta radiation of ^{153}Sm is emitted at maximum energies of 640, 710, and 810 keV (32.2%, 49.6%, and 17.5% respectively) with an average beta particle energy of 233 keV. These particles penetrate tissue only over a relatively short distance of 1-2 mm, allowing the delivery of high doses of radiation to the tumor while sparing surrounding normal tissue. ^{153}Sm has a half-life of 46 hours, but that portion of the drug not complexed to bone is completely eliminated through the kidneys within 6 hours of administration.

4.2 ANIMAL STUDIES

The efficacy of ^{153}Sm -EDTMP has been demonstrated in both murine and canine models of osteogenic sarcoma. Winderen et al. reported that ^{153}Sm -EDTMP could effectively treat orthotopic human osteosarcoma implanted in immunodeficient mice (5). Early studies with canine osteogenic sarcoma showed that ^{153}Sm -EDTMP caused a period of reversible pancytopenia. Subsequently, forty dogs with spontaneous osteogenic sarcomas were treated with one or two doses of 1 mCi/kg ^{153}Sm -EDTMP. Small lesions, metastatic lesions, and lesions of the axial skeleton responded well, while large lesions with minimal tumor bone formation responded poorly (6). The major toxicity was hematopoietic. In another study of canine osteosarcoma, there was a complete remission in 1 of 9 dogs treated with 1 mCi/kg (7). A dosimetry study in this animal model system showed that approximately 20 Gy were delivered to bone tumors by administration of 1-1.5 mCi/kg ^{153}Sm -EDTMP (8).

4.3 HUMAN STUDIES

¹⁵³Sm-EDTMP is licensed by the Food and Drug Administration for the treatment of disseminated skeletal metastases from prostate and breast cancer. In a Phase I trial of adult patients treated with doses anticipated to deliver up to 280 cGy to sites of disease, pain relief was noted in 22 of 34 patients with skeletal metastases, and stabilization or regression of the metastatic lesions occurred in 15 of 34. The only side effect was myelosuppression (9). In a Phase II study, also of adults, pain relief was noted in 14 of 23 patients, with toxicity limited to myelosuppression (10). Similar results were achieved in a Phase I/II trial of 52 patients with prostate cancer who received doses of 0.5 – 3.0 mCi/kg (11).

The first report of a patient treated for osteogenic sarcoma with ¹⁵³Sm-EDTMP was published in 1996. A 35-year-old man with a primary osteogenic sarcoma of the first lumbar vertebra had a local relapse with significant pain and neurologic dysfunction related to spinal cord compression. He was treated with 2 doses of ¹⁵³Sm-EDTMP, 8 weeks apart, at approximately 1 mCi/kg per dose. He had significant, though transient (6 months), improvement in neurologic function and resolution of his pain (12). Additionally, a group from Munich reported their results treating 6 patients who had unresectable localized or metastatic osteogenic sarcoma with a combination of multi-agent chemotherapy, ¹⁵³Sm-EDTMP, and external beam radiation. The 3 patients treated with all of these agents (chemotherapy, ¹⁵³Sm-EDTMP, and external beam radiation) had responses, including one 3-plus year survivor (13).

A report from the Mayo Clinic described the results of a Phase I trial of high dose ¹⁵³Sm-EDTMP in patients with metastatic osteogenic sarcoma using stem cell support to bypass dose limitations imposed by myelosuppression, which was the sole toxicity reported. Thirty patients were treated, and all of them had either a reduction in opiate requirement or complete resolution of their pain. The maximally tolerated dose on that study was 30 mCi/kg. This group measured the dose of radiation delivered to the tumor, and found that dose delivered correlated with the dosage of ¹⁵³Sm-EDTMP administered (14).

Our group has recently completed a two-phase study of eleven heavily pre-treated patients with osteosarcoma, who received tandem dosing of ¹⁵³Sm-EDTMP (15-16). With regards to patient outcome, though the study was terminated early based on protocol definition of clinical response, six patients showed radiographic stabilization. Toxicity was limited to hematologic suppression, manageable with stem cell transfusion support. We demonstrated that the total dose delivered to the tumor site with the initial “tracer” administered activity, and the subsequent higher, “treatment” administered activity displayed a strictly proportionate, linear relationship within each patient. Using this relationship, we plan to calculate the “treatment” administered activity necessary to achieve a planned total dose to tumor based on dosimetry mapping of the initial “tracer” activity. This allows a more accurate calculation and prediction of tumor exposure from a given infusion of ¹⁵³Sm-EDTMP.

These studies suggest that a significant quantity of ¹⁵³Sm-EDTMP can be given with manageable toxicity, and that treatment infusion needed to reach a planned total dose delivered to the tumor site can be predicted based on an individual patient’s dosimetry results after the initial tracer dose. Depending on the individual patient’s total dose exposure, we could then combine ¹⁵³Sm-EDTMP treatment with supplemental external beam radiation therapy. A recent paper reported that reasonable response times >3-5 years resulted with mean radiation dosing of 68.4 Gy (17). With tumoricidal dosing estimated to be 70-75 Gy, a proportion of this could be

given infusionally as ^{153}Sm -EDTMP, potentially decreasing the intensity of external beam radiation therapy needed to reach these target doses and minimizing local tissue damage.

The primary goal of this study will be to examine tumor response after radiation treatment via a combination of ^{153}Sm -EDTMP and external beam radiotherapy. A well-described characteristic of calcified osteogenic sarcoma lesions, as well as many bony metastases, is that despite necrosis or lack of viable tumor being detectable on histologic analysis, the tumor frequently does not shrink by radiographic imaging. Therefore the major clinical endpoint in evaluating clinical response will be lack of progression (stable disease or better by RECIST criteria). The favorable, manageable toxicity profile of ^{153}Sm -EDTMP would meet the needs of our study population of poor-risk, heavily pre-treated patients who might not otherwise be candidates for additional toxic therapy. This novel strategy of combined infusional and external-beam radiotherapy might prove to be an effective means for local control and offer significant clinical benefit.

4.4 HYPOXIA AND [^{18}F] FLUOROMISONIDAZOLE (^{18}F -MISO) PET

Hypoxia has been demonstrated in solid tumors and has been shown to be associated with resistance to chemotherapy, as well as potentially contributing to a more aggressive and invasive phenotype. One of the key players thought to orchestrate these changes is hypoxia inducible factor 1-alpha (HIF1- α), which acts as a transcription factor inducing production of numerous proteins that alter microenvironment and promote growth, neoangiogenesis, and invasion. Yang et al investigated HIF1- α expression in osteogenic sarcoma, and noted that 80% of tumors expressed HIF1- α , with increased microvessel density, a marker for hypoxia and likely resultant angiogenesis within tumor tissue (18). [^{18}F]-MISO PET scanning has been described in the literature as a tool to measure hypoxic areas in tumors (19). [^{18}F]-MISO accumulates in viable tissues preferentially when $\text{pO}_2 < 10$ mmHg and is dependent on nitroreductase activity within the cell. It is not dependent on blood flow, and is not retained in necrotic tissue. Studies have demonstrated changing hypoxia status in irradiated non-small cell lung cancer using this modality, as well as several papers in soft tissue sarcoma and head and neck cancers (20-24).

In our previous work, we demonstrated that changes in SUVmax measured by traditional FDG-PET scanning did not correlate with response to therapy. This suggests that FDG-PET may underestimate treatment response, possibly due to post-therapy inflammatory changes. Our interest in using [^{18}F]-MISO PET is two-fold. Our main question is whether tumors with higher [^{18}F]-MISO PET indices prior to treatment (increased hypoxia) might display less response to our proposed radiation therapy, which might ultimately allow us to predict patients likely to benefit. We also will investigate whether an improvement in oxygenation status (decrease in [^{18}F]-MISO indices) following treatment might correlate with histologic response to therapy given the lack of uptake demonstrated in necrotic tissue. In an effort to improve sensitivity of the [^{18}F]-MISO assessment of hypoxia and ensure attention to tumor volumes, we will combine the imaging with traditional [^{18}F]-FDG PET.

5.0 ELIGIBILITY CRITERIA

5.1 INCLUSION CRITERIA

5.1.1 Subjects will be between 10 and 65 years of age, inclusive.

5.1.2 Patient must have unresectable primary tumor or metastases (including tumors with an intralesional resection.)

5.1.2.1 For Stratum 1, patients must have a confirmed histologic diagnosis of osteosarcoma.

5.2.1.2 For Stratum 2, any histologically confirmed solid tumor diagnosis is eligible.

5.1.3 Patients must have measurable disease that is avid for phosphonate compounds as demonstrated by a positive Tc-99m bone scan. Not all lesions must be positive on bone scan.

5.1.4 Adequate organ function:

5.1.4.1 Adequate renal function, defined as a measured creatinine clearance >70 ml/min/1.73 m² or normal radioisotope GFR.

5.1.4.2 Adequate hematologic function, defined as a platelet count $>50,000/\text{mm}^3$ and an absolute neutrophil count $> 500/\text{mm}^3$

5.1.5 Life expectancy of > 8 weeks

5.1.6 Karnofsky performance status $> 50\%$

5.1.7 Patients must have recovered from the effects of any prior chemotherapy, as determined by the treating physician and studyteam, based in part on organ function defined above.

5.1.8 A stem cell product collected prior to the infusion of ^{153}Sm -EDTMP must be available, either by peripheral stem cell mobilization or bone marrow harvest prior to trial entry. A minimum of 2×10^6 CD34⁺ cells/kg ideal body weight is required.

5.1.9 The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent to become a study subject has been obtained, in accordance with institutional policies approved by the U.S. Department of Health and Human Services.

5.2 EXCLUSION CRITERIA

5.2.1 Patients must not be pregnant or breastfeeding. Sexually active patients are strongly advised to use accepted, effective forms of contraception.

5.2.2 Patients who have received prior radiotherapy to all areas of current active disease are ineligible.

5.3 INFORMED CONSENT

Informed consent will be obtained from the parents or legal guardian of minor children. Patients over the age of 18 years will provide their own informed consent. Either assent or

consent will also be obtained at a developmentally appropriate level from subjects that are minor children.

5.4 REGISTRATION

To register a patient, the following documents should be completed by the Research Nurse or Study Coordinator and faxed (410-502-9933) or emailed (crocc@jhmi.edu) to the Coordinating Center:

- Fax cover sheet
- Registration form
- Signed patient consent form
- HIPAA authorization form
- Eligibility screening checklist

Copy of required screening tests and scansThe Coordinating Center will then verify eligibility and complete the registration process, by:

- Assigning a patient study number
- Registering the patient on the treatment portion of the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office
- Faxing or e-mailing the patient study number to the participating site
- Calling or e-mailing the research nurse or data manager at the participating site, verbally confirming registration and the last eligible start date for treatment.

6.0 TREATMENT PLAN

6.1 PRETREATMENT EVALUATION

6.1.1 History and physical examination, including symptoms, height, weight, and body surface area

6.1.2 Laboratory evaluation, including CBC with differential and platelet count, comprehensive metabolic panel, urinalysis, 24-hour urine for creatinine clearance, phosphorus, magnesium, LDH, serum C-telopeptides (JHH Pathology test code 6315) and parathyroid hormone. Alkaline phosphatase and LDH will be fractionated if elevated to determine the contribution of bone isoforms (Quest referral tests).

6.1.3 Radiographic evaluation: chest X-ray, Tc-99m bone scan, and other imaging that may include CT, MRI, and/or PET/CT scans of primary tumor and any large metastases.

6.1.4 Cardiac evaluation: baseline EKG to be obtained prior to treatment.

6.1.5 As part of the study protocol, subjects will undergo a pre-treatment [^{18}F]-MISO/[^{18}F]-FDG whole body PET scanning as delineated in section 6.2.4.

6.2 OVERALL TREATMENT PLAN

This is a treatment protocol to establish the safety and efficacy of radiation therapy consisting of high-dose ^{153}Sm -EDTMP and external beam radiotherapy for the treatment of high-risk osteogenic sarcoma and solid tumors with bony metastases. The primary endpoint will be clinical response of tumor lesions, defined as either stable disease or decrease in the size of the tumor by radiographic imaging (which may include CT or MRI) using RECIST 1.1 criteria. Progression will be defined as appearance of new lesions or expansion of current lesions by 20% as per RECIST 1.1 criteria. In some patients, additional information on clinical response may be obtained from histology (percent tumor necrosis) in cases where patients proceed to resection or biopsy following radiation therapy. Other treatment endpoints include progression-free and overall survival. We will obtain post-treatment [^{18}F]-MISO and [^{18}F] FDG PET scans to be analyzed but these images will not be used to define clinical response.

The first administered activity of ^{153}Sm -EDTMP will be a low “tracer” infusion administered at 1 mCi/kg on Day 1. Using the 3-dimensional dosimetry package 3D-RD, we will perform three-dimensional dosimetry using SPECT images after administration of the “tracer” activity to determine the distribution of dose delivered to the tumor and the surrounding normal tissues. As quickly as feasible (goal is within seven days), using the dosimetric results from the tracer administration, a combined treatment plan will be designed aimed at delivering the target dose to the entire tumor. This plan will be designed using methodology uniquely available at Hopkins (3D-RD software); we will import the 3-dimensional absorbed dose map resulting from ^{153}Sm -EDTMP therapy, adjusted to correspond to the fractionation schedule used in external beam radiotherapy, into the external beam planning system (Pinnacle), by fusing (registering) the SPECT/CT and absorbed dose map with the external beam planning CT, allowing a treatment plan to be generated from the combination of (1) scaling of the tracer absorbed dose map to the requisite ^{153}Sm therapeutic activity and (2) external beam fields designed to optimally complement the radiopharmaceutical absorbed dose map to deliver a target of 75 Gy to each and every tumor voxel while respecting normal organ constraints (25).

The first portion of the combined plan, that is, the second, “treatment” ^{153}Sm -EDTMP infusion, will then be implemented on Day 8. Maximum activity administered will be 30 mCi/kg, which is the maximally tolerated dose permitting recovery of myelosuppression with auto-stem cell infusion (14). After the “treatment” infusion, SPECT scans will again be performed to confirm total dose delivered and subsequently adjust the external beam portion of the treatment plan, as necessary. External beam radiotherapy will begin as early as possible between Days 15 and 22. The total dose to be used will be modified based on surrounding tissue tolerances. On Day 24, previously harvested autologous peripheral blood or bone marrow stem cells will be infused in order to ameliorate the expected myelosuppression. External beam radiation therapy will not be administered on Day 24 (anticipated to be a Friday), nor on Days 25 or 26, in order to provide time for infused hematopoietic stem cells to home to the bone marrow and leave the circulation.

Patients will be reimaged one month following completion of external beam radiation by CT/MRI for evidence of clinical response (defined as stable disease or better by RECIST 1.1 criteria) or disease progression. In the event of progression of a single lesion, local therapy such as radiofrequency ablation or cryoablation may be provided so that the response of stabilized lesions can continue to be monitored. If suspicious lesions remain on

thoracic CT scan or on MRI of the primary site after the completion of therapy, further evaluation by biopsy may be clinically indicated, and potentially surgical intervention pursued if persistent disease is found. Percent necrosis of any resected tumor will be evaluated pathologically.

6.2.1 Stem cell collection

Although ifosfamide mobilization is preferred, any method for obtaining autologous hematopoietic stem cells (HSC) is acceptable. The timing of stem cell collection is at the discretion of the treating physician, as long as stem cells are collected prior to administration of $^{153}\text{Sm-EDTMP}$.

Recommended, but not required, approach if prior collection not available and no evidence of Ifosfamide resistance: Peripheral blood stem cells will be collected as per standard protocols after a cycle of Ifosfamide given as a single agent, at a dose of $3 \text{ g/m}^2/\text{day}$ for 5 days with MESNA. The MESNA will be administered according to institutional standards.

G-CSF will be administered daily upon completion of the chemotherapy at a dose of $10 \mu\text{g/kg/day}$ subcutaneously. Peripheral blood CD34^+ cell count will be monitored daily beginning on Day 7 after chemotherapy is completed, or when ANC begins to rise, and pheresis will be performed when indicated.

Collection of $5 \times 10^6 \text{ CD34}^+$ cells/kg will be the goal, with the product split into 2 aliquots and stored frozen until needed. If more than $6 \times 10^6 \text{ CD34}^+$ cells/kg are collected, three aliquots will be stored. Pheresis on consecutive days will be performed if necessary to meet this target. A minimum collection of $2 \times 10^6 \text{ CD34}^+$ cells/kg will be required for treatment with $^{153}\text{Sm-EDTMP}$.

If peripheral stem cell collection is not feasible or cell mobilization is inadequate, bone marrow harvest in the operating room under general anesthesia will be an alternative source and may be performed as per standard protocols.

6.2.2 Radiation Dosimetry

^{153}Sm SPECT/CT imaging with the CT acquisition in high resolution mode will be collected at approximately 4 hours after infusion of the “tracer” dose; SPECT/CT imaging with CT acquisition in attenuation correction (low-res.) mode will be performed at 24 and 48 hours post-infusion to determine the absorbed dose for a given administered activity of $^{153}\text{Sm-EDTMP}$. The 24 and 48 hour post-infusion SPECT/CT scans can be obtained any time one and two days after treatment, as long as the specific number of hours post-infusion is recorded. We will use the in-house developed software package, 3D-RD, to calculate lesion absorbed dose maps that will be transferred to the external radiotherapy software so that a combined radiotherapy treatment plan is generated. The combined treatment plan will be used to determine the administered activity and external beam radiation needed to deliver a total combined, absorbed dose 75 Gy to the lesion while respecting toxicity constraints to adjacent dose-limiting tissues. This approach is based on

previous studies showing that lesion absorbed scales with administered activity (16). We have also demonstrated the ability to adjust for dose rates by using the biologic effective dose (BED) formalism and thereby incorporate radiopharmaceutical therapy into an external radiotherapy treatment plan (25-26). ^{153}Sm planar imaging of the abdomen will be performed at 1 and 2 hours after the “treatment” infusion to allow an assessment of radiation delivered to kidneys. SPECT/CT imaging will also be collected at three later time-points after the “treatment” administration: approximately 4 hours, 24 hours, and 48 hours. The 24 and 48 hour post-infusion scans can again be obtained at any time on the first and second day after treatment, as long as the specific number of hours post-infusion is recorded. If lesion dosimetry from the therapy study is inconsistent with the low dose projection, the combined treatment plan will be revised accordingly. This treatment dose will not exceed 30 mCi/kg, the dose previously delineated by Anderson, et al as the maximally tolerated dose for reversible hematologic toxicity (14).

Based on experience and patient tolerability, the number and frequency of SPECT/CT scans may be modified over the course of the trial.

6.2.3 Autologous Peripheral Blood Stem Cell or Bone Marrow Infusion

Sixteen days after administration of the treatment dose of ^{153}Sm -EDTMP, autologous peripheral blood stem cells or bone marrow will be reinfused according to standard institutional protocols.

6.2.4. Acquisition of ^{18}F -MISO/ ^{18}F -FDG PET *imaging*

We plan to obtain investigational imaging of tumor hypoxia using ^{18}F -MISO in combination with traditional ^{18}F -FDG PET imaging. Following treatment, we will analyze the ^{18}F -MISO PET data to determine any correlation to clinical response defined by traditional RECIST criteria with CT/MRI imaging, and percent necrosis as determined by histology as detailed in section 10.1.

Protocol: Patients will undergo FDG-PET/CT according to standard protocols, and ^{18}F -MISO PET scanning as per the described protocol (21). Images will be compared side-by-side to ensure accurate inclusion of tumor fields, as described by Rajendran (23). Four venous blood samples will be collected five minutes apart to normalize Tumor/Blood ratios as described in reference 23. Additionally, ratios between tumor and contralateral soft tissue, as well as tumor/adjacent muscle will be obtained. Ratios of greater than 1.2 will be considered hypoxic. Ratios will be converted to milliliter volume to measure hypoxic tumor volume. We will discount any lesions occurring in the liver or bladder from study due to inaccurate readings previously reported.

6.2.5 Planning and administration of external beam radiation therapy

Initial planning CTs for radiation therapy will be performed just prior to initiation of therapy. After each samarium infusion, if tolerable, the patient will be placed in a reproducible treatment position using an appropriate immobilization device based on treatment site while data from SPECT/CT is obtained. Alternatively, the two CT

components will be co-registered and combined fields generated. Subsequent radiation therapy will be planned to reach a total minimum dose to tumor of 75 Gy as described (25). The dose of supplemental EBRT will be decided after determination of the EBRT dose equivalent delivered by the ^{153}Sm in order to reach a total minimum dose to the gross tumor volume (GTV) of 75 Gy. GTV will be defined as gross tumor on the two planning CT scans. A margin of 1.5 cm will be added to the GTV to create a clinical target volume (CTV) which will be modified to exclude adjacent normal tissues that are not involved by tumor. An additional margin of 5 mm-1 cm will be placed around the CTV to create a planning target volume (PTV) and will be dependent on treatment site and immobilization technique.

Conformal techniques such as intensity-modulated radiotherapy (IMRT) or tomotherapy will be used to plan the supplemental EBRT. The goal will be to achieve a target supplemental EBRT dose coverage of $\text{D}_{95} > 95\%$ to the PTV. Normal tissue dose constraints based on QUANTEC will be applied and respected. Standard protocols apply for supportive care based on site irradiated, and toxicity will be closely documented.

6.3 ON-STUDY EVALUATION

- 6.3.1 Dosimetric studies by ^{153}Sm SPECT/CT to be assessed at approximately 4, 24, and 48 hours after injection of tracer dose of ^{153}Sm -EDTMP; SPECT/CT will also be collected at approximately 4, 24, and 48 hours following the therapeutic administration of ^{153}Sm -EDTMP. Scans can be obtained at any time on the first and second day after infusion of ^{153}Sm -EDTMP, as long as the specific number of hours post-infusion is recorded.
- 6.3.2 Complete evaluation, including history and physical exam, vital signs, weights, and laboratory evaluation including complete blood counts and a complete metabolic panel, Mg and Phosphorous to be performed weekly until hematopoietic recovery and until recovery from therapy-related toxicities.
- 6.3.3 Because of the risk of renal and bladder toxicity from the excretion of ^{153}Sm -EDTMP that is not adsorbed to tumor, care will be taken to monitor patients closely for urinary tract toxicity. Prior to treatment, patients will have a complete urinalysis, measurement of BUN and creatinine, and 24- hour urine collection for creatinine clearance. These tests will be repeated as clinically indicated based on urinary symptoms and at the completion of therapy.
- 6.3.4 Restaging evaluation to include radiologic imaging by CT or MRI of the primary tumor and metastases, follow up [^{18}F]-MISO/[^{18}F]-FDG PET, plain radiographs of primary lesion, and Tc-99m bone scan. These studies will occur approximately one month after completion of external beam radiotherapy. Based on our prior experience with [^{18}F]-FDG PET and the lack of correlation between clinical response and SUV levels, we will not use [^{18}F]-MISO/[^{18}F]-FDG PET SUVmax measurements to determine clinical response while the patient is receiving treatment.

- 6.3.5 CT scan of chest and Tc-99m bone scan every 4 months after completion of therapy for one year, then every 6 months for 1 year, and then yearly for 3 years. Thereafter scans will be repeated only as clinically indicated.
- 6.3.6 Evaluation for long-term skeletal toxicity will be performed every 6 months for the first 4 years after completion of therapy, and will include alkaline phosphatase and LDH (bone fractions), serum C-telopeptide and parathyroid hormone levels, and bone density scans.
- 6.3.7 If any lesions are resected after patient has completed radiation therapy, percent necrosis will be determined by the pathologist and recorded.

6.4 Schedule of Assessments

Table 1. Schedule for On-Study Patient Evaluations.

(Note this does not include additional clinically appropriate testing in the setting of stem cell rescue and routine monitoring while on external beam radiation therapy.)

Evaluation	PreTx ¹	1 st Sm	2 nd Sm	External Beam Radiation				
Week	-3- 0	1	2	3	4	5	>	
1 st Day of Week	-21 - 0	1	8	15	22	24	29	
H&P, Vital signs and Wt	x	x	x	X ³	x		x	
Ht and BSA (baseline only)	x							
CBC	x		x	x ³	x		x	
CMP	x		x	x ³	x		x	
Ca/Phosphorus/Mg	x		x	x	x		x	
Alk Phos ⁴ , LDH ⁴	x							
C-telopeptides (JHH Path test code 6315) + PTH	x							
Ionized Ca level ⁵		x	x					
Urinalysis	x							
Creatinine Clearance ⁶	x							
Hematopoietic stem cell (HSC) collection ⁷	x							
EKG ⁸	x	x	x					
Chest X-ray	x							
CaCO ₃ (oral)		X ⁹	X ⁹					
Mycotic disease prophylaxis ¹⁰ (oral)		x	x	x	x	x	x	
<i>Pneumocystis carinii</i> pneumonia prophylaxis ¹¹ (oral)		x	x	x	x	x	x	
Stem Cell Infusion						x		
Rad Onc Planning CT	x ¹²							
¹⁵³ Sm planar imaging of abdomen			x ¹³					
SPECT/CT		X ¹⁴	x ¹⁴					
CT/MRI ¹⁵	x							
CT chest								
^{99m} Tc-Bone Scan	x							
Plain radiographs of primary lesion	no							
¹⁸ F-FDG PET/CT	x							
¹⁸ F-MISO PET	x							

Table 1 Footnotes: ¹ Pre-treatment radiographic evaluation must be obtained within 3 weeks of study entry. Pre-treatment laboratory studies must be obtained within 2 weeks of study entry. Blood tests need not be repeated prior to first ¹⁵³Sm-EDTMP treatment.

² Start between D15 and D22

³ Weekly H&P, labs til CBC and AE recovery

⁴ Alk phosphatase and LDH will be fractionated if elevated. (Quest lab referral tests)

⁵ Check prior to administration of ¹⁵³Sm-EDTMP

⁶ Measured creatinine clearance or nuclear medicine GFR. Do not use calculated creatinine clearance.

⁷ Ifos + Mesna x 5 days recommended. Peripheral CD-34 cell count done daily starting at chemo D7 until high enough for pheresis.

⁸ Obtain at screening, pre and at completion of ¹⁵³Sm-EDTMP infusions on Days 1 and 8.

⁹ CaCO₃ to be administered prior to ¹⁵³Sm-EDTMP; 1000 mg calcium carbonate the morning of each samarium infusion

¹⁰ Days 1-75

¹¹ From Day 1 until 6 months after completion of therapy

¹² Timing of Rad Onc Planning CT relative to study entry at discretion of treating physician, and coordinated by Radiation Oncology.

¹³ ¹⁵³Sm planar imaging of the abdomen will be performed at 1 and 2 hours after the “treatment” infusion.

¹⁴ SPECT/CT scans to be obtained after ¹⁵³Sm-EDTMP infusions at approximately 4, 24, and 48 hrs post each injection of ¹⁵³Sm-EDTMP. The 24 and 48 hour post- infusion SPECT/CT scans can be obtained any time one and two days after treatment, as long as the specific number of hours post-infusion is recorded.

¹⁵ Choice of imaging modality and location as clinically indicated. To include primary tumor and any large metastases.

¹⁶ Four tubes of venous blood drawn 5 minutes apart; drawn only in conjunction with FMISO PET scans, and are to be processed by nuclear medicine as a part of that scan protocol.

Table 2. Schedule for Post Treatment and Follow Up Patient Evaluations

Evaluation	Post Tx Assessment (30 days after final tx)	Months post End				
		4	6	8	12	18
H&P, Vital signs and Wt	X	X	X	X	X	X
CBC ¹	X	X	X	X	X	X
CMP ¹	X	X	X	X	X	X
Phosphorus, Mg	X	X	X	X	X	X
Alk Phos ² , LDH ²	X		X		X	X
C-telopeptides (JHH Path test code 6315)	X		X		X	X
PTH	X		X		X	X
Bone density scan			X		X	X
Urinalysis	X					
Creatinine Clearance ³	X		X		X	X
Chest X-ray		X		X	X	X
Mycotic disease prophylaxis ⁴	X (thru D75)					
Prophylaxis for <i>Pneumocystis carinii</i> pneumonia (PCP) ⁵	X	X	X			
CT/MRI ⁶	X	X		X	X	X
CT chest		X		X	X	X
^{99m} Tc-Bone Scan	X	X		X	X	X
Plain radiographs of primary lesion	X					
¹⁸ F-FDG PET/CT	X			X	X	
¹⁸ F-MISO PET	X			X	X	
Blood samples with F-MISO PET ⁷	X			X	X	

ly H&P, labs til CBC and AE recovery

² Alk phosphatase and LDH will be fractionated if elevated. (Quest lab referral tests)

³ Measured or nuclear medicine GFR

⁴ Days 1-75

⁵ From Day 1 until 6 months after completion of therapy.

⁶ Choice of imaging modality and location as clinically indicated. To include primary tumor and any large metastases.

6.5 SUPPORTIVE CARE GUIDELINES

6.5.1 ^{153}Sm -EDTMP infusions

- 6.5.1.1 Stable central venous access is required, preferably through the placement of a double-lumen central venous catheter. Intravenous fluids will be administered to assure line patency pre ^{153}Sm -EDTMP administration and to thoroughly flush line post ^{153}Sm -EDTMP administration.
- 6.5.1.2 Administration of ^{153}Sm -EDTMP will be performed under the direction of the institution's Radiation Oncology Department/Division, according to standard procedures for the delivery of radioactive isotopes. Medical Physics personnel will be present for the entire procedure. The appropriate dose will be removed from the supplier's vial with a protected syringe and will be administered over 1-2 minutes followed by flushing of IV line to ensure line is cleared of samarium. Isolating patient and shielding from radioactivity is not necessary for ^{153}Sm -EDTMP administration.
- 6.5.1.3 Patients will take 1000 mg calcium carbonate the morning of samarium infusion to decrease the risk of transient samarium-related hypocalcemia. Ionized calcium level will be checked prior to administration of the ^{153}Sm -EDTMP. Additional calcium gluconate may be given as needed for ionized calcium less than 1.2 mmol/L. Calcium gluconate will be available for treatment of symptomatic hypocalcemia.
- 6.5.1.4 A 12-lead EKG will be checked prior to administration of ^{153}Sm -EDTMP. A second 12-lead EKG will be checked at the completion of the infusion. If any EKG changes are noted or patients develop symptoms attributable to hypocalcemia, patients may be discharged with additional calcium carbonate and arrangements made for recheck of calcium levels the following day.

6.5.2 Auto-stem cell infusion and recovery

Pediatric and adult guidelines for preventing and managing complications of autologous HSC transplant patients in effect at the time of treatment should be followed and may supersede the following recommendations.

- 6.5.2.1 Blood component support. All blood products will be irradiated to prevent graft-versus-host disease. Transfusions with leukocyte-poor packed red blood cells will be given as needed to maintain the hematocrit greater than 25%. Platelets will be given as needed to maintain the platelet count above 10,000, or higher as clinically indicated.
- 6.5.2.2 Infectious prophylaxis. Patients should be given prophylaxis against mycotic disease from Day 1 through Day 75. Suspected or documented fungal infections should be promptly treated according to standards for transplant recipients. Patients

should receive effective prophylaxis for *Pneumocystis carinii* pneumonia, from Day 1 until 6 months after treatment is completed.

6.5.2.3 Management of fever. Management of fever in neutropenic patients will be according to practice guidelines for the bone marrow transplant service. Broad spectrum antibiotics will be initiated, after appropriate cultures are obtained, for any fever $>38.5^{\circ}\text{C}$. Persistent unexplained fever will be treated as a presumptive invasive fungal infection.

6.5.2.4 Immunizations. Patients will not receive any immunizations for at least 6 months after completion of therapy. They will not receive any live viral vaccines until appropriate T lymphocyte counts and responses to diphtheria and tetanus vaccines have been demonstrated. Immunization of household members for influenza in the first two years after treatment will be recommended as for households of autologous BMT recipients.

6.5.3 Concomitant medications

While on study care should be taken to avoid medications that potentially will worsen pancytopenias or hypocalcemia. Additionally, patients may not receive bisphosphonate therapy while on trial.

6.5.4 Radiation therapy.

Complete consent and counseling will be specific to the radiation site and plan, and will be administered by treating radiation oncologist.

7.0 TOXICITY AND COMPLICATIONS

7.1 IFOSFAMIDE: Nausea, vomiting, anorexia, anemia, leucopenia, thrombocytopenia, hair loss, arrhythmia (rare), sleepiness, confusion (rare), seizures (rare), electrolyte imbalance, hemorrhagic cystitis, renal failure or insufficiency, myocardial necrosis (rare), scarring of the bladder or lungs, infertility, and second malignancy (very rare).

7.2 MESNA: Nausea, vomiting, stomach pains, headache, diarrhea, allergic reactions, and pains in the arms, legs, and joints (all very rare).

7.3 ^{153}Sm -EDTMP: Pain at the tumor site, slow bone growth (rare) or bone deformity (rare). The EDTMP component may cause hypocalcemia and may very rarely cause reactions such as wheezing, low blood pressure, hives, or trouble breathing.

7.4 STEM CELL INFUSION: Hypertension, nausea, bradycardia, garlic-like odor to the breath (all due to residual DMSO used as a cryopreservative).

7.5 G-CSF: headache, fever, chills, decreased appetite, pains in bones, chest, belly or joints, and rash.

7.6 EXTERNAL BEAM RADIOTHERAPY: The specific risks associated with external beam radiotherapy depend on the sites to be treated and the techniques that are used. These will be discussed in detail at the time of treatment by the radiation oncologist.

8.0 AGENT INFORMATION

8.1 ¹⁵³SM-EDTMP

¹⁵³Samarium is a beta- and gamma-emitting lanthanide element. It has 3 principal beta emissions of 640 keV, 710 keV, and 810 keV maxima. These medium energy beta particles are tumoricidal. It also emits a gamma photon of 103 keV that allows for scintigraphic imaging. ¹⁵³Samarium is chelated with EDTMP (also known as lexidronam), a bone seeking tetraphosphonate compound. The chelated complex, ¹⁵³Sm-EDTMP, is supplied sterile and pyrogen-free from the manufacturer (EUSA Pharma) under the trade name Quadramet. It is dissolved in a saline solution (typically 10 ml total volume) that is infused intravenously over a 1-2 minute period.

8.2 IFOSFAMIDE (IFEX)

NSC-109724. Commercially available.

Formulation: Lyophilized powder, 1 g and 3 g per vial.

Storage: Room temperature. *Reconstitution:* Reconstitute 1 gm vial with 20 ml sterile water and 3 g vial with 60 ml sterile water, to a final concentration of 50 mg/ml. Further dilution with NS, D5W, or Lactated Ringer's is acceptable. *Stability:* Discard reconstituted drug after one week at 30° or 3 weeks at 5°C.

Toxicities: Myelosuppression. Alopecia. Nausea and vomiting. Hemorrhagic cystitis, and acute tubular necrosis. Lethargy, confusion, somnolence, excitement, disorientation, and hallucination. Transient liver function abnormalities.

8.3 MESNA (SODIUM 2-MERCAPTOETHANESULFONATE)

NSC-113891. Commercially available.

Formulation: 1,000 mg/10 mL multidose vials which contain 10.4 mg/mL of benzyl alcohol as a preservative.

Storage: Room Temperature. *Reconstitution:* Dilution of Mesna with NS, D5W, or Lactated Ringer's is acceptable. *Stability:* MESNA is not light-sensitive, but is oxidized to diMESNA when exposed to oxygen. Non-preserved ampules should be used immediately after opening, while benzyl alcohol-preserved vials may be stored and used for 8 days. After further dilution for administration, either product is chemically stable for at least 24 hours. Lack of an antimicrobial preservative suggests that the non-preserved product should be used within 6-8 hours after diluted for administration. *Toxicities:* Bad taste in the mouth, nausea and vomiting, diarrhea. Young children receiving high doses of benzyl alcohol (> 99 mg/kg/day) may develop the gasping syndrome manifested by gasping, metabolic acidosis and multiple

organ system failure. Benzyl alcohol is the preservative in multidose vials of MESNA. It results from inability to adequately conjugate benzoic acid with glycine, a metabolic pathway poorly developed under 8 weeks of age.

9.0 TREATMENT EVALUATION

9.1 DEFINITIONS

9.1.1 Radiologic Response

9.1.1.1 Complete response: Complete resolution of all disease by radiologic imaging (CT or MRI).

9.1.1.2 Partial response: > 50% reduction in the sum of the products of perpendicular tumor diameters.

9.1.1.3 Minor response: A 25-50% reduction in the sum of the products of the tumor diameter without the emergence of new lesions. No individual lesion progressing more than 25% in a single dimension

9.1.1.4 Stable disease: No progressive disease.

9.1.1.5 Progressive disease: Emergence of new lesions or progression of any lesion by more than 20% in a single dimension.

9.1.2 Histologic Response

9.1.2.1 Complete response: 100% necrosis.

9.1.2.2 Good response: $\geq 90\%$, but $< 100\%$, necrosis.

9.1.2.3 Poor response: $< 90\%$ necrosis.

9.1.3 Clinical Response

Patients will be considered a clinical response if they have stable disease or any radiologic response by RECIST 1.1 criteria. Dates of progression or death will also be recorded in order to calculate progression-free and overall survival. Toxicities will be graded according to the Bearman criteria for bone marrow transplant studies and according to the NCI Common Terminology Criteria for Adverse Events version 4.0.

9.2 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study for patient or parent choice, or for excessive toxicity at the discretion of the principal investigators.

10.0 SERIAL MEASUREMENTS (see Table 1 in Section 6.3)

- 10.1 Time of entry into the study: ^{99m}Tc bone scan, X-rays and/or CT or MRI evaluation of the primary and metastatic lesions (specific modality at clinician's discretion). A pre-treatment [^{18}F]-MISO/ [^{18}F]-FDG PET scan will be obtained for baseline readings as part of study.
- 10.2 One month after completion of external beam radiotherapy: repeat initial imaging modality and territories, as well as any other imaging clinically indicated. [^{18}F]-MISO/ [^{18}F]-FDG PET will be obtained at that time as well.
- 10.3 Subsequent follow up as per Table 1. Scans will be repeated every 4 months for the first year after completion of therapy, every 6 months during the second year after therapy, and yearly thereafter for a total of 5 years.
- 10.4 At progression, patient will undergo repeat [^{18}F]-MISO/[^{18}F]-FDG PET.

11.0 STATISTICAL CONSIDERATIONS

11.1 OVERVIEW

This protocol will assess the proportion of clinical tumor responses, defined as progression-free survival at 6 months, and the toxicities associated with high-dose ^{153}Sm -EDTMP (MTD at 30 mCi/kg) after an initial lower dose of the agent along with external beam radiation therapy in patients with high-risk osteogenic sarcoma.

Primary objective: The primary objective of this study is to determine if the addition of external beam radiation therapy to infusional ^{153}Sm -EDTMP can delay the progression of target lesions. The primary endpoint is 6-month progression free survival (PFS). It is a combined effect of the entire treatment. To be evaluable, patients must meet all eligibility criteria, including signing a consent form, and have completed treatment according to protocol without major deviations. Patients who are enrolled but unevaluable will be replaced on the study. Only patients enrolled on Stratum 1 (i.e., with a diagnosis of osteosarcoma) will be evaluated for the Primary Objective.

Secondary objectives:

1. Describe the short and long-term toxicity profile of combined treatment with ^{153}Sm -EDTMP and external beam radiation therapy.
2. Estimate the local control rate. (Stratum 1 only)
3. Determine the overall survival (OS). (Stratum 1 only)
4. Describe the distribution of absorbed doses delivered to each targeted lesion and the distribution of equivalent uniform doses delivered to each patient.
5. Model the relationship between absorbed doses and time to progression.
6. Determine the correlation of hypoxic volume and maximum tumor/blood ratio obtained by [^{18}F]-MISO PET scanning with patient outcomes.

11.2 STUDY DESIGN

This is a single-arm study with 2 strata: Stratum 1 for patients with osteosarcoma, and Stratum 2 for patients with other high risk solid tumors. Stratum 2 is exploratory in nature, and the goal of including these patients is to facilitate accomplishing secondary objectives related to toxicity and the feasibility of administering this treatment regimen to solid tumor patients. If possible, we will, however, use patients on Stratum 2 to estimate response rates of tumors other than osteosarcoma. For Stratum 1, 6-month PFS as the primary endpoint. The study will pre-specify target lesions for each patient in Stratum 1 that will be used to assess PFS, with the intention that every lesion radiographically evident at the time of enrollment will be a target lesion. Events will be the first disease progression at any of the target lesions or death from any cause. All patients treated on Stratum 1 will be included in the determination of PFS, regardless of treatment modification or discontinuation. The design will include interim analyses for futility if it seems unlikely that the treatment has sufficient activity. The historical PFS in 11 patients treated with ^{153}Sm -EDTMP similar to how we are proposing, but without the external beam component, was 15.8%. For this study of ^{153}Sm -EDTMP plus external beam radiation therapy, a 6-month PFS of 35% would be the lowest that would be considered acceptable, and PFS that is convincingly worse than this would be considered grounds for discontinuing further study. The non-parametric Kaplan-Meier estimate will be used to monitor the PFS function. After 8 patients have been enrolled, the design will include an interim analysis for futility that could halt the trial if it seems likely that this regimen does not have sufficient clinical activity. The study is designed to stop if we are 80% certain that the 6-month PFS is below 15%.

11.3 STATISTICAL ANALYSIS PLAN

11.3.1 Estimate the PFS for subjects treated on Stratum 1.

Sample size: The primary measure of efficacy will be PFS at 6-months for Stratum 1 patients. In specific, the 6-month PFS for this treatment will be compared to a reference of 15.8% (hazard rate = 0.308/person-month i.e. median of 2.25 months). In patients with metastatic osteosarcoma a 6-month PFS of 35% would be considered promising, and is the benchmark for this study. Assuming exponential survival, 4 patients per year will be accrued for 5 years (20 total), one year of additional follow-up, and a one-sided 0.05 alpha level test, the sample size of 20 will have 82% power to detect a hazard ratio of 1.76.

Early stopping guideline for safety: The study will be monitored after every patient for non-hematologic grade 4 toxicities following initiation of external beam radiation therapy. This stopping rule for toxicity will hold enrollment if the posterior probability of risk being larger than 0.2 is 75% or higher. The prior for this toxicity monitoring rule is beta (1, 5). This distribution means that our prior guess at this type of grade 4 toxicity is 16.7%, and there is 95% probability that it is between 0.51% and 52.2%. The operating characteristics of the stopping rule are shown below and are based on 5000 simulations:

Toxicity stopping rule:

Study termination if:	2 AEs	3 AEs	4 AEs	5 AEs	6 AEs
And number of patients between:	2 - 3	4 - 7	8 - 12	13 - 16	17 - 20

Operating characteristics of stopping rule based on 5000 simulations:

True Toxicity Risk	Prob. Declare Treatment Too Toxic	Avg. Sample Size
0.05	1.0%	19.8
0.10	6.4%	19.2
0.15	17.1%	17.9
0.20	33.7%	16.2
0.25	54.0%	13.8
0.30	69.1%	12.0
0.35	82.9%	9.7
0.40	92.6%	7.9

Early stopping guideline for futility and simulations: Simulation is used to demonstrate the operating characteristics of the study for a sample size of 20. The study will be monitored for futility with a primary endpoint of 6-month PFS. The non-parametric Kaplan-Meier estimate will be used to estimate the PFS function at 6-months. After 8 patients have been enrolled, the design will include an interim analysis for futility that could halt the trial if it seems likely that the treatment does not have sufficient clinical activity.

The sample size of 20 and the study design operating characteristics assume a 5 year accrual period with an additional follow-up of one year. The null 6-month PFS is 15.8%. We have designed the study to stop early only if the posterior probability of 6-month PFS being less than 0.15 is 80% or higher. Simulations were carried out with exponential survival and staggered patient entry. We assume on average 1 patient will enter the study every three months. Interim analyses begin once 8 patients have been entered on the study and occur after groups of 4 patients thereafter up to a maximum of 20 patients. The interim analysis estimates of 6-month PFS are based on analyses with an underlying Dirichlet process prior. We approximate the posterior distribution, which is actually a mixture of Beta distributions, the mixture depending on the amount of censoring, with a single Beta distribution. The parameters of this posterior Beta distribution are based on the number of failures and the effective sample size at 6-months, combined with the parameters of the prior.

The following table summarizes the operating characteristics of the futility stopping rule under various scenarios for the underlying exponential PFS, based on 5000 simulations. For futility monitoring we characterize the uncertainty of the 6-month PFS estimate with the prior: beta (1, 4). This implies that our prior guess at the 6-month PFS in this study is 20% and there is 90% certainty that the 6-month PFS is between 1.3% and 52.7%.

Table 2. Interim monitoring rule operating characteristics

6-month PFS	Prob Stop for Futility	Avg N	Estimated 6-mo PFS	lo 90% Post Int'l	hi 90% Post Int'l
0.10	0.60	14.2	0.07	0.0	0.20
0.15	0.39	16.2	0.12	0.0	0.30

0.20	0.23	17.7	0.18	0.0	0.35
0.25	0.12	18.7	0.23	0.0	0.40
0.30	0.07	19.2	0.29	0.0	0.45
0.35	0.04	19.6	0.34	0.15	0.50
0.40	0.02	19.8	0.40	0.20	0.60

Analysis for primary objective: Overall hazard rate estimates and 95% confidence intervals as well as Kaplan-Meier (KM) estimates will be used to summarize PFS over time. The 6-month PFS with 95% confidence interval will be reported.

11.3.2 Describe the toxicity profile of this regimen in the short and long-term.

Toxicities will be graded according to CTCAE v4.0 and the RTOG Cooperative Group Common Toxicity Criteria, and attributable toxicities grade 3 or higher will be recorded. For purposes of evaluation, we will consider toxicities resulting from the administration of ¹⁵³Sm-EDTMP separately from toxicities resulting after initiation of external beam radiation therapy. [However, we will hold accrual after enrollment of five patients to evaluate cumulative toxicity from the combined regimen.] Adjustments to external beam therapy in response to toxicity would be made in accordance with standard Radiation Oncology treatment protocols and clinical judgment.

11.3.3 Describe the distribution of absorbed doses delivered to each targeted lesion and the distribution of equivalent uniform doses delivered to each patient.

The total absorbed dose delivered to each targeted lesion will be limited by the tolerance of surrounding normal tissue. We will produce histograms showing the distribution of radiation absorbed doses by lesion, and summarize the results by patient for the lesion receiving the lowest absorbed dose in each patient. With a sample size of 20 patients, we will be able to estimate the proportion of patients whose lesions are all treated to an absorbed dose of ≥ 80 Gy with a precision of $\pm 23\%$.

11.3.4 Model the relationship between absorbed dose and time to progression for patients enrolled in Stratum 1.

We expect a total dose of 80 to 100 Gy to produce a local control rate of 80%, while a total absorbed dose of 60 to 70 Gy may produce a local control rate of 50 – 70%, and the local control rate would decline steeply at lower absorbed doses. We will use a generalized mixed effects model treating dose and time as fixed effects and the random effect of individual patients for the outcome of progression of each targeted lesion. If at least 10 patients have at least one lesion that receives a radiation dose with similar effectiveness to our historical control experience, and at least one lesion receiving the targeted dose, this analysis would have 80% power to demonstrate a significant dose-response with alpha 0.05.

11.3.5 Determine overall and progression-free survival for patients enrolled in Stratum 1.

Survival curves will be estimated by using the Kaplan-Meier method. Progression-free survival is defined as time from registration to the first observation (documentation) of disease progression or death. Patients who are lost to follow-up will be censored for determination of PFS on the date of their last evaluations. Overall survival is defined as time from registration to death due to any cause.

11.3.6 Determine correlation of hypoxic volume and maximum tumor/blood ratio obtained by [¹⁸F]-MISO PET scanning with patient outcomes.

Cox regression analysis will be performed to measure association between hypoxia based on HV and max T/B ratio with Kaplan-Meier survival and time-to-progression curves. Additional regression analysis will be performed to evaluate the link between hypoxic indices and uptake of ¹⁵³Sm-EDTMP and clinical response based on radiologic response and presence of necrosis on histology.

11.4 STUDY ACCRUAL

Based on prior accrual data, we anticipate enrolling five patients per year, with an expected study duration of five years.

12.0 DATA RECORDING, MANAGEMENT, AND MONITORING

12.01 To register eligible patients on study, the investigator will fax the completed registration form to the Johns Hopkins Oncology center Clinical Research Office at 410-614-1328.

12.02 Informed consent must be signed by the patient or in the case of a minor, the parent or legal guardian.

12.03 If a patient does not receive protocol therapy, the patient is removed from protocol. Reasons for cancellation must be submitted in writing to the Principal Investigator. Once a patient has been given protocol treatment, all forms must be submitted.

12.04 Case report forms, including dosimetry, toxicity and response evaluation will be completed in a timely manner.

12.05 This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee.

The PI is responsible for monitoring the study. Data must be reviewed to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study.

The PI will be responsible for maintaining the clinical protocol, reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the continuing renewal report

submitted to the IRB and to the trial monitoring review group. Content of the continuing renewal report at a minimum should include year-to-date and full trial data on: accrual and eligibility, protocol compliance, treatment administration, toxicity and ADR reports, response, survival, regulatory compliance, compliance with prearranged statistical goals. The report should be submitted in a timely manner according to the schedule defined by Johns Hopkins Medicine Institutional Review Board.

12.1 REPORTING OF ADVERSE REACTIONS

12.1.1 Definitions

12.1.1.1 An **adverse event** is any new, undesirable medical occurrence or change of an existing condition in a subject that occurs during treatment (which may include a specified post treatment period), whether or not considered to be product related. Abnormal laboratory findings considered by the reporting physician to be clinically significant, e.g. those that are unusual or unusually severe for the population being studied, should be recorded as adverse events.

12.1.1.2 A **serious adverse event** is defined by regulatory/clinical criteria. It is one that suggests a significant hazard or side effect, regardless of the investigator's or sponsor's opinion on the relationship to study material. This includes, *but may not be limited to*, any event that (at any dose):

- is fatal;
- is life threatening (places the subject at immediate risk of death);
- requires in-patient hospitalization or prolongation of existing hospitalization; or
- is persistent and results in significant disability/incapacity.

12.1.2 Investigator's Reporting Obligations

12.1.2.1 Grade 4 (life-threatening) or grade 5 (fatal) adverse events that are unexpected (no listed on the package label) with an attribution of possible, probable, or definite must be reported to the FDA within 10 business days.

12.1.2.2 Reports to the FDA should be submitted in writing (FDA Form 3500 MEDWATCH) to:

10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-4636-3332
Fax 1-888-463-6332
www.fda.gov/medwatch

with a copy simultaneously submitted to the Johns Hopkins Institutional Review Board.

12.1.2.3 Johns Hopkins Institutional Review Board reporting requirements: The Organization has the responsibility to report unanticipated problems involving

risk to subjects or others under [Policy 103.6\(b\)](#), serious or continuing non-compliance under [Policy 103.7](#), and suspension or termination of approved research under [Policy 113.1](#), to the appropriate agencies. The Institutional Official (IO) is authorized as the individual who will submit reports when an IRB has made a determination under the three cited policies. In cases where the IRB and IO determine that additional information is required before submitting a final report, a preliminary report may be made to the appropriate officials, supporting federal agency (as applicable), OHRP, and FDA (as applicable), within one month of the IRB's determination.

12.1.2.4 A draft preliminary or final report will be prepared for review by the IO and General Counsels (GCs). The draft report will contain the following information:

- The nature of the event
- The findings of the organization
- The actions taken by the organization and IRB, including plans to protect the rights and welfare of the participants
- The reasons for the organization's and IRB's actions
- The plans for continued oversight or investigation or action.

The draft report will be finalized by the IO and the GCs. The IO will sign the report within 20 days of the agreed upon final revision of the report. The final report will be submitted to the OHRP if the research is conducted, funded, or overseen by DHHS; to FDA, if the research is regulated by FDA; and to other agencies that are signatories to the Common Rule [\[1\]](#), if the research is conducted, funded or overseen by that agency. A copy of the report will be sent to the reviewing IRB, ORA if the project is funded by an outside sponsor, Risk Management (if applicable), and the PI. The IO may determine the report should be provided to the Director of the department in which the PI is appointed as faculty and the Dean of the School of Medicine. If the event involves unauthorized use, loss, or disclosure of PHI, a copy will be sent to the HIPAA Privacy Officer. 12.7.2.3 All toxicities should be recorded on the flow sheet.

12.1.2.5 Notify the P. I. immediately of any fatal toxicity.

12.2 EARLY STOPPING RULE

Data will be reviewed on an ongoing basis. An early stopping rule for safety is described above (Section 11.3.1). For the stopping rule, the requirement for hospitalization in the first five weeks after samarium for temporary hematopoietic, infectious, or GI toxicities will not *per se* be considered a defining criterion of seriousness of an adverse event.

This is a Level 1 study under the SKCCC CRO Data and Safety Monitoring Plan. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on

the rate of subject accrual and the progress of the study. Trial monitoring and reporting will be done through the Clinical Research Review and Monitoring Committee (CRC).

13.0 MULTICENTER GUIDELINES

Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

14.0 REFERENCES

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