

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0517

RANDOMIZED PHASE III TRIAL TO EVALUATE RADIOPHARMACEUTICALS AND ZOLEDRONIC ACID IN THE PALLIATION OF OSTEOBLASTIC METASTASES FROM LUNG, BREAST, AND PROSTATE CANCER

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RTOG 0517

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <http://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0517

Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer

SCHEMA

S		R	
T	Site of Primary	A	Arm 1
R	1. Lung	N	*zoledronic acid, 4 mg IV, monthly, plus
A	2. Breast	D	vitamin D and calcium supplement
T	3. Prostate	O	
I		M	Arm 2
F	Number of Bone Mets	I	*zoledronic acid, 4 mg IV, monthly plus
Y	1. ≤ 2	Z	vitamin D and calcium supplement, plus
	2. > 2	E	**single dose of Sr-89 or Sm-153
			within 6 weeks of randomization

*Zoledronic acid is given monthly for an indefinite period of time and discontinued at the discretion of the treating physician.

**Dose: Sr-89 = 4 mCi; Sm-153 = 1 mCi/kg body weight

Patient Population: (See Section 3.0 for Eligibility)

Histologically proven diagnosis of solid tumor malignancy of lung, breast, or prostate; bone metastases must be visible on bone scan performed within 4 weeks prior to study entry.

Required Sample Size: 352

RTOG Institution # _____

RTOG 0517

ELIGIBILITY CHECKLIST (7/11/06) (7/25/07) (9/28/07)

Case # _____

(page 1 of 3)

- _____(Y) 1. Does the patient have a histologically confirmed diagnosis of lung cancer, breast cancer, or prostate cancer?
- _____(Y) 2. Has a history and physical examination been done within 8 weeks prior to registration?
- _____(Y) 3. Has a bone scan been done, with bone metastases visible on the scan, within 4 weeks prior to registration or if the bone scan is equivocal, does an MRI, PET, plain film, etc. confirm metastases?
- _____(Y) 4. Has a dental evaluation been done within 8 weeks prior to registration and recorded on the dental exam checklist?
- _____(Y) 5. Has a CBC/differential/platelets been done within 2 weeks prior to registration showing adequate bone marrow function per Section 3.1?
- _____(Y) 6. Has a serum creatinine and total bilirubin been done within 2 weeks prior to registration with results as outlined in Section 3.1?
- _____(Y) 7. Is the patient 18 or older?
- _____(Y/N) 8. Is the patient female and of childbearing potential?
- _____(Y) If yes, has a pregnancy test (urine dipstick or serum) been done within 2 weeks prior to registration?
- _____(Y) 9. Is the patient's performance status rated 0, 1 or 2 (breast or prostate primaries) or 0 or 1 (lung primaries) using the Zubrod scale?
- _____(Y/N) 10. Has the patient received prior external beam radiotherapy?
- _____(Y) If yes, was the last treatment 14 or more days prior to registration?
- _____(Y/N) 11. Has the patient received prior treatment with CyberKnife?
- _____(Y) If yes, was the last treatment 14 or more days prior to registration?
- _____(Y/N) 12. Has the patient received prior oral bisphosphonate therapy?
- _____(Y) If yes, have the oral bisphosphonates been discontinued prior to registration?
- _____(N) 13. Has the participant received prior treatment with Strontium-89 or Samarium-153 for bone metastases?
- _____(Y/NA) 14. If participant is a woman of childbearing potential, has she agreed to practice an adequate mean of birth control throughout treatment in this study?
- _____(Y/NA) 15. If participant is male, has he agreed to practice an adequate means of birth control throughout treatment in this study?

(Continued on next page)

RTOG 0517

RTOG Institution # _____

RTOG 0517

ELIGIBILITY CHECKLIST (3/8/07) (7/25/07) (9/28/07)

Case # _____

(page 2 of 3)

- _____(N) 16. Does the participant have brain metastases or spinal cord compression?
- _____(Y/N) 17. Does the participant have painful bone metastases?
- _____(Y) If yes, has the participant been successfully treated and pain been stable for at least 2 weeks after that treatment? (Stable pain is defined as a patient response of 1, 2, or 3 on Questions 4 and 5 of the BPI.)
- _____(Y/N) 18. Was participant ever treated with IV bisphosphonates?
- _____(Y) If yes, is the cumulative length of treatment \leq 6 months?
- _____(Y/N) 19. Has the participant been treated with calcitonin, mithramycin or gallium nitrate?
- _____(Y) If yes, was this \geq 2 weeks before registration?
- _____(N) 20. In the past 6 months, has the participant shown any signs of uncontrolled congestive heart failure; hypertension refractory to treatment; or symptomatic coronary artery disease?
- _____(N) 21. Does the participant have any current dental problems (or problems which occurred in the 4 weeks prior to registration), such as infection of the teeth or jawbone; dental or fixture trauma; a current or prior diagnosis of osteonecrosis of the jaw; exposed bone in the mouth; previous or current slow healing after dental procedures?
- _____(N) 22. Has the participant had any dental surgery, such as extraction or implants, in the 6 weeks prior to registration?
- _____(N) 23. Is the participant known to have AIDS?
- _____(N/NA) 24. Is the participant pregnant or lactating?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician

(Continued on the next page)

RTOG Institution # _____

RTOG 0517

ELIGIBILITY CHECKLIST (7/11/06) (11/7/08)

Case # _____

(page 3 of 3)

- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Randomization Date: This date will be populated automatically.
- _____ 18. Specify site of primary (Lung, Breast, or Prostate)
- _____ 19. Specify number of bone mets (≤ 2 or > 2)
- _____ (N/Y) 20. Did the patient agree to participate in the Quality of Life component of the study?
_____ If no, please specify the reason from the following:
 - 1. Patient refused due to illness
 - 2. Patient refused for other reason: specify _____
 - 3. Not approved by institutional IRB
 - 4. Tool not available in patient's language
 - 5. Other reason: specify _____

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

Completed by _____

Date _____

1.0 INTRODUCTION

Each year, more than 100,000 patients in the U.S. develop bone metastases from spread of their primary cancer.¹ Bone is the third most common site of metastatic disease after liver and lung, and spread to bone is associated with considerable morbidity. This includes bone pain and fracture, spinal cord compression, and hypercalcemia. The incidence of bone metastasis is expected to increase over the next decade as patient survival improves due to advances in anticancer therapy. This will make the treatment of this problem more important in the overall management of the surviving cancer patient.

1.1 Bone Metastases

The majority of skeletal metastases arise from primary tumors of the thyroid, kidney, lung, prostate, and breast, with the latter two accounting for about 80% of metastatic bone disease.² While all bones can be affected, the most common site of disease spread is the spine with the subsequent development of spinal cord compression. In advanced breast cancer, a majority of skeletal events will occur every 3 to 4 months resulting in significant morbidity and impaired quality of life.³

The pathogenesis of metastatic bone disease follows a common pathway. Cells from a primary tumor enter the circulation, travel to a distant bony site, and enter the sinusoids of the bone marrow cavity. After establishing a blood supply and migrating to the endosteum, the metastatic cancer cells stimulate and alter the activity of osteoclasts or osteoblasts and a pattern of lytic or blastic bone destruction is set up.⁴ In normal tissue, bone remodeling is a balance between osteoblastic activity, which promotes bone production, and osteoclastic activity, which breaks bone down.⁵ These activities are controlled by paracrine factors, including tumor necrosis factor alpha and beta, interleukin-1, and prostaglandins, all of which may have control over the process of bone metastasis growth.⁶ Since bone is a dynamic tissue that undergoes remodeling throughout life, tumor cells that disrupt this process can precipitate destruction of bone.

Therapy for bone metastases has usually been considered palliative and is given to reduce symptoms caused by disease progression.⁷ Syndromes related to bone metastases include pain, impaired mobility, decreased bone marrow function, fractures, hypercalcemia, and spinal cord compression. Treatment usually does not start until the patient presents with a complication from the metastatic site of disease. At that point, multiple therapies can be instituted, including pain medication, radiation therapy, radiopharmaceuticals, orthopedic stabilization, bisphosphonates, hormonal manipulation and chemotherapeutic treatment.⁸⁻¹³

While all of the above treatments appear to be somewhat effective in the treatment of complications caused by bone metastases, bisphosphonates appear to be more effective in slowing or reversing the progression of skeletal metastases. This has been well documented in both metastatic breast cancer and multiple myeloma.^{1,5,14,15} Bisphosphonates, which are pyrophosphate analogues, are potent inhibitors of pathologic bone resorption and significantly reduce osteoclastic activity.^{3,14,16} Reduced osteoclastic activity is achieved by several cellular mechanisms that appear to induce apoptosis. Trials using either pamidronate or clodronate in metastatic breast cancer have shown reductions in complications from lytic metastases as well as reduction in the development of new skeletal metastases.^{17,18} Furthermore, some trials suggest that bisphosphonates may play a role in relieving bone pain, although that is more controversial.¹⁶ To date, the majority of clinical trials examining the effects of bisphosphonates have been in patients with metastatic breast cancer or multiple myeloma, although metastases from other primaries have been investigated with encouraging results.^{19,20} Patients with metastatic prostate cancer were found to have fewer fractures and other bone complications when they took zoledronic acid than when they took a placebo.²¹ Unfortunately, the reductions in bone complications did not delay disease progression, lengthen survival, or improve quality of life and were not recommended as routine therapy in this group of patients. However, this is still an open area of investigation for prostate cancer patients.

1.2 Zometa® (Zoledronic Acid)

Bisphosphonates differ from one another by substitution of active side chains on their phosphorous - carbon - phosphorous structural backbone.²² First generation bisphosphonates (etidronate and clodronate) have alkyl or halide side chains. The second generation bisphosphonate, Aredia® (pamidronate disodium), is characterized by a side chain with an amino terminal group and has an increased antiresorptive potency of 10-100 times the previous generation.²²⁻²³ Zometa®, a 3rd generation bisphosphonate, is 2-(imidazol-1-yl-hydroxyethane-1,1-bisphosphonic acid) in the form of its monohydrate. This compound is characterized by a side

chain consisting of an imidazole ring group. Zometa® is a more potent inhibitor of osteoclasts than earlier bisphosphonates. In the 1,25-dihydroxyvitamin D3-induced in vivo hypercalcemia model of parathyroidectomized rats, Zometa® is 850 times more potent than pamidronate and more than four orders of magnitude more potent than either clodronate or etidronate.²⁴⁻²⁵ In addition, Zometa® is two orders of magnitude more potent than pamidronate in inhibiting the release of calcium from mouse calvaria in vitro irrespective of the stimulus [1,25(OH)2D3-, PTH, PTHrP, prostaglandin-E2, or IL-1B].²⁶ Zometa® has little effect on bone mineralization in vitro, and this drug has the largest therapeutic ratio between the desired inhibition of calcium resorption and the unwanted inhibition of mineralization in vitro of all the bisphosphonates.²⁴

Phase I clinical trials also have provided evidence of the potency of Zometa® to inhibit osteoclastic bone resorption.²⁷⁻²⁸ In rat models of osteopenia, the bisphosphonates alendronate, pamidronate, and Zometa® prevented bone loss in the distal femur and lumbar vertebra as measured by chemical analysis and/or bone density. Of the three bisphosphonates, Zometa® was the most potent, being 10-30 times more potent than alendronate and 120 times more potent than pamidronate. In addition, animal studies have shown that long term Zometa® therapy is well tolerated and prevents bone loss and increased skeletal turnover, and this response is dose related.²⁹ Also, an ongoing phase II study indicates that long term therapy with Zometa® administered in short 15 minute infusions is well tolerated.²⁵

Bisphosphonates have been administered orally, intravenously, and in the case of clodronate, intramuscularly. Because all bisphosphonates have nephrotoxic potential, those normally used intravenously are administered as an infusion rather than by bolus injection. Renal failure has been reported in three patients receiving rapid infusions of etidronate and clodronate at relatively high doses.³⁰ Even when lower doses of these agents are infused slowly, they can still cause transient changes in renal function.³¹ Data from animal toxicology experiments indicate that kidney damage is the only consistent abnormality following repeated intravenous infusions of pamidronate (Aredia®). In general, the effects were more pronounced following bolus injections than after intravenous infusions, and daily treatment resulted in more pronounced effects than weekly administration. In these experiments, necrosis of the proximal renal tubules was demonstrated, often accompanied by elevated levels of serum creatinine and/or urea.^{32, 33-34} However, nephrotoxicity has not been reported in clinical trials with pamidronate (Aredia®) because, due to its higher potency, approximately 10-fold lower doses are required than for etidronate or clodronate. This could be important if the mechanism of kidney damage is the formation of complexes with calcium, since fewer complexes would presumably be formed at lower unit dosages.

Zometa® has little effect on bone mineralization in vitro. In rat models, the rapid absorption and adherence of Zometa® to bone results in its quick and complete elimination from the circulation. Gastrointestinal absorption of Zometa® is poor, and does not exceed 5% of a dose of 1.5 mg/kg. The drug is not metabolized, and is cleared rapidly from the circulation and excreted via the kidneys within 24 hours. Zometa®, therefore, has the largest therapeutic ratio between the desired inhibition of calcium resorption and the unwanted inhibition of mineralization in vitro characteristic of all bisphosphonates.²⁴

The pre-clinical safety (toxicology) profile of Zometa® is, in general, similar to that of other bisphosphonates, including pamidronate (Aredia®), but the compound appears to produce fewer and/or less severe adverse events at what are considered to be pharmacologically effective doses. The renal and intestinal tolerability profiles of pamidronate and Zometa® have been demonstrated to be similar in animal models, despite Zometa® being the much more potent inhibitor of bone resorption.

1.3 Radiopharmaceuticals

Radiopharmaceuticals have been used in patients with diffuse bony metastases for many years. The administration of beta-emitting radiopharmaceuticals with significant affinity for bone was initially suggested as a treatment modality in the 1950s, and the first available compound was phosphorus-32 (P-32).³⁵ Silberstein has extensively reviewed the existing published literature.³⁶ Although it was clear that that P-32 represented an effective agent resulting in palliation in 50%-70% of patients in this disease category, it was associated with hematologic toxicity and, because of this, has fallen into disuse.

Strontium-89 (Sr-89) and Samarium-153 (Sm-153) are effective agents in the palliation of painful bony metastases without the associated hematological toxicity of P-32. All three radioisotopes share certain characteristics. First, they are incorporated into bone by virtue of their elemental nature or through the chemical properties of an attached ligand. Next, the therapeutic radiation emitted is that of low-energy electrons (beta emissions) as opposed to gamma radiation, which is normally used in nuclear medicine imaging. Finally, they are preferentially incorporated into bony lesions undergoing repair compared with normal bone.

Sr-89 imitates calcium *in vivo*, localizing in proliferation bone without marrow or leukocyte incorporation that occurs when P-32 enters into the cells' phosphate biochemical pathway. Sr-89 is a pure beta emitter with maximum beta energy of 1.4 MeV and a half-life of 50.6 days. It rapidly washes out of healthy bone with a half-life of 14 days.³⁷⁻³⁸ Sm-153 is similar to Sr-89 in that it emits low-energy electrons. It differs in that it is a pyrophosphate analog rather than a calcium analog, and therefore, behaves more like a bisphosphonate. Its half-life is short (46 hours vs. 50.5 days with Sr-89) and theoretically, should have limited radiation dose to bone marrow. It has rapid renal clearance, and uptake is proportional to the number of skeletal metastases.³⁹⁻⁴⁰ There does not appear to be any effect of bisphosphonates on the subsequent skeletal uptake of Sm-153.⁴¹ There has never been a head-to-head randomized trial between strontium and samarium, and for this study, it will be presumed that either radioisotope is acceptable for treatment.

There are several clinical trials and retrospective reports on the use of Sr-89 and Sm-153 that were reviewed by Mertens, et al.⁴² In essence, a single intravenous injection of isotope given over 2 to 3 minutes provides pain relief in more than 50% of patients who have diffuse painful bony metastases. This relief usually comes after 2 to 7 days and may last several months. The beauty of these agents is that they target all osteoblastic metastases by convergence on reactive bone sites with a very low concentration in the surrounding normal bone, bone marrow, and other structures.⁴³

It has been shown in several trials that radiopharmaceuticals can be given along with cytotoxic chemotherapy without causing additional hematologic toxicity necessitating dose reductions.⁴⁴⁻⁴⁵ One randomized trial has shown that the addition of a radiopharmaceutical to a chemotherapy regimen has improved overall survival in androgen-independent prostate cancer patients.⁴⁶ There is now an ongoing trial comparing consolidation therapy with or without Sr-89 following induction chemotherapy in androgen-independent prostate cancer (NCI# MDA-3410). There have also been bone metastases from other cancers successfully treated with radioisotopes for palliation.⁴⁷

The difficulty with the regimen in MDA-3410 is that it requires patients to undergo a considerable amount of cytotoxic chemotherapy prior to receiving the radioisotope. All patients in the proposed study will receive zoledronic acid as a primary treatment. Half of the group will receive a single dose of a radioisotope. Patients may receive any other type of therapy including cytotoxic therapy, hormonal therapy, or additional radiation therapy (except for treatment of bone metastases).

1.4 Health-Related Quality of Life and Utilities

Skeletal related events (SREs), defined in this study as a pathological bone fracture, spinal cord compression, surgery to bone, or radiation to bone, have important and significant effects on measures of health-related quality of life. SREs after radiation therapy have been shown to be independent, clinically significant events for patients as measured by the Functional Assessment Cancer Therapy-General (FACT-G), the Brief Pain Inventory (BPI), and the EuroQol-5 Dimension (EQ-5D). The clinical impact of SRE's in patients with advanced prostate cancer who have widespread bone metastases is well known. A recent study⁴⁸ of this group of patients (n=248) treated with zoledronic acid versus placebo showed a clinically meaningful and statistically significant decline in physical well-being after experiencing a pathologic fracture and receiving radiation therapy for it. Furthermore, functional and combined well-being also declined significantly after experiencing a pathologic fracture and undergoing palliative radiation for bone pain. There also were meaningful and significant declines in preference and utility scores after radiation and fracture. Pain intensity declined after radiation but not after other SREs. The quality of life component of this study will include three measures, the Functional Assessment of Cancer Therapy-General (FACT-G), The Brief Pain Inventory (BPI), and the EuroQol (EQ-5D). These assessments will be administered at 4 weeks and at 3, 6, and 12 months.

RTOG is planning to conduct three trials related to the prevention or delayed progression of SREs (RTOG 0517, 0518, 0431). This will be the first cooperative group attempt to coordinate all three studies from inception to assess similar symptoms/quality of life/utility endpoints among related studies. Assessments will be conducted using the same instruments (as appropriate) at the same time points. The planned meta-analysis will provide additional value-added benefit from the three trials in terms of assessing multimodality therapy to reduce in the incidence of SREs in patients at risk due to cancer or cancer therapies.

1.4.1 *The Functional Assessment of Cancer Therapy – General (FACT-G)*

The FACT-G is a commonly used instrument measuring general quality of life (QOL) reflecting symptoms or problems associated with malignancies across 4 scales: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); and functional well-being (7 items).⁴⁹ Patients rate all items using a five-point rating scale ranging from "not at all" to "very much." The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, relationship with doctor, emotional well being, functional well-being, and disease-specific concerns. Six additional experimental items request information regarding how much each dimension affects QOL, using a "0" (not at all) to "10" (very much so) rating scale. The FACT-G scale is able to distinguish metastatic from non-metastatic disease, $F(1,334) = 5.38, p < .05$. It also distinguishes between stage I, II, III and IV disease, $F(3,308) = 2.94, p < .05$, and between inpatients and outpatients from different centers, $F(2,411) = 17.0, p < .001$. On the FACT-G, sensitivity to disease status was restricted to the Physical ($p < .01$) and Functional ($p < .001$) subscales. Concurrent validity is supported by strong Pearson correlations with the Functional Living Index - Cancer (.79) and a patient-completed version of the QOL Index (.74). Initial evidence for construct validity is supported by: 1) moderate to high correlations with mood state as measured by the Taylor Manifest Anxiety Scale (.57) and a shortened version of the Profile of Mood States (.69); 2) moderate correlation with activity level (negative direction of coefficient because of reverse scaling) as measured by the Eastern Cooperative Oncology Group five-point rating (-.56), and a small correlation with social desirability as measured by a shortened version of the Marlowe-Crowne Social Desirability Scale. The FACT-G has been written at the 4th grade reading level, and patients can complete it in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, <http://www.facit.org/translation/licensure.aspx>.

1.4.2 *The Brief Pain Inventory (BPI) (9/28/07)*

The BPI, developed by Daut, et al, was modeled after the McGill Pain Questionnaire.⁵⁰⁻⁵¹ The BPI is a seventeen-item patient self rating scale assessing demographic data, use of medications, as well as sensory, and reactive components of pain. Respectable reliability has been demonstrated over short intervals using test retest item correlation; worst pain, $r = .93$; usual pain, $r = .78$; pain now, $r = .59$. Evidence of validity of the BPI comes from several sources. The relationship between use of pain medications and overall pain ratings was examined. The percentage of patients taking pain medications increased with high pain ratings. Significance was demonstrated between increased medication use and high pain ratings for both narcotic ($x = 28.17, df = 3, p < 0.002$) and non narcotic ($x = 23.75, df = 3, p < 0.002$) pain relievers. Validity of the BPI was also supported by the moderate correlation between worst pain intensity ratings and ratings of interference with six areas of activity and mood ($r = .245$ to $.478, p < 0.02$ for all but social relationships were $p < 0.05$). And finally, there is a logical pattern in the differences in inter-correlations among various pain and activity interference measures for different diseases.⁵⁰

The BPI includes items that will address components of sensory pain including severity, location, chronicity and degree of relief due to therapy. The BPI also has items that address reactive pain components including depression, suffering and perceived availability of relief. The BPI's ease of translation (validated in 12 languages) and brief administration have made it a frequently used tool in clinical trials in which reduction or prevention of pain are primary or secondary outcome measures, and it is considered the FDA standard for a pain assessment tool. Sites also will document patients' opioid use.

1.4.3 *The EuroQol-5 Dimension (EQ-5D)*

The EQ-5D is a method for obtaining valuations of health-related quality of life (HRQOL), preference and utility scores to be used as an adjustment to survival, and may be used in future cost-utility analysis. It is a two-part questionnaire that takes approximately 5 minutes to complete.⁵² The first part consists of 5 items covering 5 dimensions including: mobility, self

care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the five dimensions, generating 243 (35) health states to which unconsciousness and death are added.⁵³ The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm 10 point-interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale and best imaginable health state is scored as 100 at the top. Both the five-item index score and the VAS score are transformed into a utility score between 0 “Worst health state” and 1 “Best health state”. Either the index score or the VAS score can be used in the quality adjusted survival analysis, or enter the cost-utility equation, depending on the health state(s) of interest.⁴¹ Quality adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time [U= sum of quality (qi) of health states K times the duration (si) spent in each health state].⁵⁵ The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at <http://www.euroqol.org/>

2.0 OBJECTIVES

2.1 Primary Objective

To determine if the addition of a radionucleotide (Strontium-89 [SR-89] or Samarium-153 [Sm-153]) to bisphosphonates for patients with asymptomatic or stable symptomatic bone metastasis will delay the time to development of malignant skeletal related events (SREs), defined as a pathological bone fracture, spinal cord compression, surgery to bone, or radiation to bone.

2.2 Secondary Objectives

- 2.2.1 To determine the rate of SREs at one year;
- 2.2.2 To determine overall survival;
- 2.2.3 To determine the effect of each treatment arm on quality of life;
- 2.2.4 To determine the effect of each treatment arm on pain control;
- 2.2.5 To evaluate resource utilization and cost effectiveness of each treatment arm.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED.

3.1 Conditions for Patient Eligibility (7/25/07) (11/7/08)

- 3.1.1 Histologically or cytologically proven diagnosis of solid tumor malignancy of lung, breast, or prostate prior to registration;
- 3.1.2 Appropriate diagnosis for protocol entry, based upon the following minimum diagnostic workup:
 - 3.1.2.1 History/physical examination within 8 weeks prior to registration;
 - 3.1.2.2 Bone scan within 4 weeks prior to registration; bone metastases must be visible on the scan. Other scanning modalities, such as MRI, PET scan, or plain radiography, may be used only to confirm the bone scan, e.g., in the event of an equivocal bone scan.
 - 3.1.2.3 Dental evaluation according to the dental exam checklist (carried out by the investigator, the investigator’s designee, or by a qualified dental professional [dental hygienist or dentist]), including history of dental surgery (e.g., extraction or implant) within 8 weeks prior to registration and recorded on the dental exam checklist; **Note:** If the patient has received prior oral bisphosphonate therapy and has had a prior dental evaluation within 8 weeks of registration, the evaluation should not be repeated.
 - 3.1.2.4 CBC/differential within 2 weeks prior to registration, with adequate bone marrow function defined as follows:
 - WBC \geq 2400 cells/mm³;
 - ANC \geq 1,800 cells/mm³;
 - Platelets \geq 60,000 cells/mm³;
 - Hemoglobin \geq 8.0 g/dl (**Note:** The use of transfusion or other intervention to achieve the required hemoglobin is permitted).
 - 3.1.2.5 Serum creatinine $<$ 3 mg/dL (265 μ mol/L) within 2 weeks prior to registration;
 - 3.1.2.6 Total bilirubin $<$ 2.5 mg/dL (43 μ mol/L) within 2 weeks prior to registration;
 - 3.1.2.7 Pregnancy test (urine dipstick or serum) for women of childbearing potential within 2 weeks prior to registration;
- 3.1.3 \geq 18 years of age;
- 3.1.4 Zubrod performance status 0-2 for patients with breast or prostate primaries; Zubrod performance status 0-1 for patients with lung primaries;

- 3.1.5 Patients receiving systemic chemotherapy or hormonal therapy are eligible for this study. **See Sections 6.0 and 7.0 for further details. Note: All patients must complete external beam radiation therapy ≥ 14 days prior to registration.** If patients have undergone CyberKnife treatment, treatment must be completed ≥ 14 days prior to registration.
- 3.1.6 Patients may have received prior oral bisphosphonate therapy, such as Fosamax® or similar medications. Duration of bisphosphonate treatment prior to study entry must be documented, and all bisphosphonates other than the study drug must be discontinued prior to registration.
- 3.1.7 Women of childbearing potential and male participants must agree to practice an adequate means of birth control throughout their participation in the study.
- 3.1.8 Patient must sign study specific informed consent prior to study entry.
- 3.2 Conditions for Patient Ineligibility (7/25/07) (9/28/07)**
- 3.2.1 Patients with brain metastases and/or spinal cord compression are excluded. **Note:** Patients with no evidence of disease in the brain after treatment for brain metastases are eligible.
- 3.2.2 Patients with painful bone metastases are not permitted until these bone metastases are successfully treated (for example by external beam irradiation) prior to registration, and the patient has stable pain for at least 2 weeks after that treatment (Stable pain is defined for this study as a patient response of 1, 2, or 3 on Questions 4 and 5 of The Brief Pain Inventory (BPI) [see Appendix V]).
- 3.2.3 Prior treatment with Strontium-89 or Samarium-153 for bone metastases.
- 3.2.4 Treatment for more than 6 months with IV bisphosphonates prior to study entry;
- 3.2.5 Treatment with calcitonin, mithramycin, or gallium nitrate within 2 weeks prior to registration
- 3.2.6 Severe, active co-morbidity, defined as follows:
 - 3.2.6.1 Evidence in the six months prior to study entry of uncontrolled congestive heart failure, hypertension refractory to treatment, or symptomatic coronary artery disease;
 - 3.2.6.2 Current, active dental problems within 4 weeks of registration, including infection of the teeth or jawbone (maxilla or mandible); dental or fixture trauma; current or prior diagnosis of osteonecrosis of the jaw (ONJ); exposed bone in the mouth; or slow healing after dental procedures;
 - 3.2.6.3 Dental surgery (e.g., extractions, implants) within 6 weeks of study entry and while receiving study treatment; for patients who require dental surgery, there are no data to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw (ONJ) [see Section 7.2.4].
 - 3.2.6.4 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- 3.2.7 Pregnant or lactating patients are excluded, as treatment may be harmful to embryos and/or nursing infants.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

- 4.1 **Required Evaluations/Management**
Note: Failure to perform one or more of these tests may result in assessment of a protocol violation.
 - 4.1.1 **For Arm 2 patients**, two weeks prior to receiving a radiopharmaceutical:
 - WBC ≥ 2400 cells/mm³;
 - ANC ≥ 1,800 cells/mm³;
 - Platelets ≥ 60,000 cells/mm³;
 - Serum creatinine < 3 mg/dL (265 μmol/L)
 - 4.1.2 If the patient consents to participate in the quality of life component of the study, sites are required to administer baseline quality of life questionnaires: Functional Assessment of Cancer Therapy-General (FACT-G); Brief Pain Inventory (BPI); and The EuroQol (EQ-5D).

5.0 REGISTRATION PROCEDURES

- 5.1 *Preregistration Requirements for Zoledronic Acid*
 - 5.1.1 **U.S. and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution's first case:
 - IRB approval letter;

- Federalwide Assurance (FWA) number;
- For Canadian sites: Health Canada's TPD Forms.

5.1.2 Note: International sites must receive written approval of submitted LOI forms (http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf) from RTOG Headquarters prior to submitting documents to their Local Ethics Committee for approval.

Approved international sites fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution's first case:

- IRB approval letter;
- Federalwide Assurance (FWA) number.

5.1.3 For the initial shipment of zoledronic acid

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). **U.S. and Canadian** institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **International institutions** must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

5.2 Registration

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user at an institution must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- A representative from the institution must complete the Password Authorization Form at <http://www.rtog.org/members/webreg.html> (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (<http://www.rtog.org>), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

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

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This

information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIOPHARMACEUTICALS

All patients on study must complete external beam radiation therapy within 14 days prior to registration. If an Arm 2 patient needs to restart radiation therapy (e.g., for lung metastasis; NO treatment of bone metastases), it is strongly recommended that radiotherapy not commence for a **minimum** of 14 days after receiving a radiopharmaceutical.

For Arm 2 patients:

- Patients must have required evaluations two weeks prior to receiving a radiopharmaceutical (see Section 4.1.1);
- If the patient is receiving chemotherapy, the therapy should not be given within 14 days of and for a **minimum** of 14 days after receiving a radiopharmaceutical;
- If the patient is receiving hormonal therapy, therapy should not be changed within 14 days prior to and for a minimum of 14 days after receiving a radiopharmaceutical.

In patients with renal dysfunction, the possible risks of administering a radioisotope should be weighed against the possible benefits.

Investigators can review ASTRO's radiopharmaceutical use guidelines available in Dillehay GL, et al. Practice guideline for the performance of therapy with unsealed radiopharmaceutical sources. *Int J Rad Oncol Biol Phys.* 64(5): 1299-1307, 2006.

6.1 Dose Specifications for Arm 2

Patients on Arm 2 will receive a single dose of Strontium-89, 4 mCi, by IV, OR a single dose of Samarium-153, 1 mCi/kg, by IV within 6 weeks of randomization.

6.2 Strontium-89 (Metastron™)

6.2.1 Formulation

Strontium-89 Chloride injection is a sterile, non-pyrogenic, aqueous solution of Strontium-89 Chloride for intravenous administration. Each milliliter contains in general strontium chloride (10.9-22 mg) and sterile water for injection. The radioactive concentration is 37 MBq/mL, 1 mCi/mL, and the specific activity is 2.96-6.17 MBq/mg, 80-167 Ci/mg at calibration. The pH of the solution is 4 – 7.5.

6.2.2 Preparation

Preparation should be done according to the manufacturer's recommendations.

6.2.3 Administration

The dose of Strontium-89 is 148 MBq, 4 mCi, administered by slow intravenous injection (1-2 minutes). Lines should be cleared by the use of at least 100 cc IV saline after the initial injection. Only one administration of Strontium-89 is permitted while the patient is on study. Administration of a second dose of radioisotope would constitute a treatment failure.

Patients who receive Strontium-89 should be advised that for several hours following administration, radioactivity will be present in excreted urine. To help protect themselves and others in their environment, precautions need to be taken for 12 hours following administration. Whenever possible, a toilet should be used, rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine gets onto clothing, the clothing should be washed separately or stored for 1-2 weeks to allow for decay of the Strontium-89.

Patients should not be released until their radioactivity levels and exposure rates comply with federal and local regulations.

6.2.4 Adverse Events

General

- A calcium-like flushing sensation has been observed in patients following a rapid (less than 30 second injection) administration. A small number of patients have reported a transient increase in bone pain at 36 to 72 hours after injection. This is usually mild and self-limiting and controllable with analgesics. A single patient reported chills and fever 12 hours after injection without long-term sequela.
- Concomitant hydration is recommended to promote the urinary excretion of Strontium-89. Appropriate monitoring and consideration of additional supportive treatment should

be used in patients with a history of congestive heart failure or renal insufficiency to ensure adequate clearance of drug.

Hematologic

- Bone marrow adverse events are common and are to be expected following the administration of Strontium-89, particularly white blood cells and platelets. The extent of the adverse event is variable. It is recommended that the patient's peripheral blood cell counts be monitored at least once every other week. Typically, platelets will be depressed by about 30% compared to pre-administration levels. The nadir of platelet depression in most patients is found between 12 and 16 weeks following administration of Strontium-89. White blood cells are usually depressed to a varying extent compared to pre-administration levels. Thereafter, recovery occurs slowly, typically reaching pre-administration levels six months after treatment unless the patient's disease or additional therapy intervenes. A single case of fatal septicemia following leukopenia was reported during clinical trials. Most severe reactions of marrow adverse events can be managed by conventional means.

Carcinogenicity

- Data from a repetitive dose animal study suggests that Strontium-89 Chloride is a potential carcinogen. Thirty-three of 40 rats injected with Strontium-89 Chloride in ten consecutive monthly doses of either 250 or 350 Ci/kg developed malignant bone tumors after a latency period of approximately 9 months. No neoplasia was observed in the control animals. Women of childbearing age should have a negative pregnancy test before administration of Strontium-89. If this drug is used during pregnancy, or if a patient becomes pregnant after taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant soon after receiving Strontium-89. Men and women patients should be advised to use an effective method of contraception after the administration of Strontium-89.

Renal and Urological

- Special precautions, such as bladder catheterization, should be taken with incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen, and the patient's environment. Urinary excretion of radioactivity occurs over about 12 hours (with 35% occurring during the first 6 hours).

6.2.5 Storage

Storage should be according to the manufacturer's recommendations. .

6.2.6 Supply

Commercially available

6.3 Samarium-153 (Quadramet®)

6.3.1 Formulation

Samarium-153 is a therapeutic agent consisting of radioactive samarium and a tetraphosphonate chelator, ethylenedi-aminetetramethylenephosphonic acid (EDTMP). Samarium-153 is formulated as a sterile, non-pyrogenic, clear, colorless to light amber isotonic solution of samarium-153 leixidronam for intravenous administration. Each milliliter contains 35 mg EDTMP•H₂O, 5.3 mg Ca [asCa (OH)₂], 14.1 mg Na [as NaOH], equivalent to 44 mg Ca/Na EDTMP (anhydrous calc.), 5-46 µg samarium (specific activity of approximately 1.0-11.0 mCi/µg Sm), and 1850 ± 185 MBq (50 ± 5 mCi) of Samarium-153 at calibration. The pH of the solution is 7.0 to 8.5. Samarium-153 emits both medium-energy beta particles and a gamma photon, and has a physical half-life of 46.3 hours (1.93 days). The gamma radiation energy is 103 keV and makes up 29% of the emitted radioactivity. The use of 1 mm of lead will decrease the external radiation exposure by a factor of approximately 1,000.

6.3.2 Preparation

Preparation should be according to manufacturer's recommendations.

6.3.3 Administration

The dose of Samarium-153 is 1.0 mCi/kg, administered intravenously over a period of one minute through a secure in-dwelling catheter and followed with a saline flush. Dose adjustments in patients at the extremes of weight have not been studied. Caution should be exercised when determining the dose in very thin or very obese patients. Concomitant hydration is recommended to promote the urinary excretion of Samarium-153, appropriate monitoring and consideration of additional supportive treatment should be used in patients with a history of congestive heart failure or renal insufficiency. Only one administration of

Samarium-153 is permitted while the patient is on study. Administration of a second dose of radioisotope would constitute a treatment failure.

Patients who receive Samarium-153 should be advised that for several hours following administration, radioactivity will be present in excreted urine. To help protect themselves and others in their environment, precautions need to be taken for 12 hours following administration. Whenever possible, a toilet should be used, rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine gets onto clothing, the clothing should be washed separately, or stored for 1-2 weeks to allow for decay of the Samarium-153.

Patients should not be released until their radioactivity levels and exposure rates comply with federal and local regulations.

6.3.4 Adverse Events (9/28/07)

General

- Samarium-153 is contraindicated in patients who have known hypersensitivity to EDTMP or similar phosphonate compounds. EDTMP is a chelating agent. Although the chelating effects have not been evaluated thoroughly in humans, dogs that received non-radioactive samarium EDTMP (6 times the human dose based on body weight, 3 times based on surface area) developed a variety of electrocardiographic (ECG) changes (with or without the presence of hypocalcemia). The extent to which samarium-153-EDTMP is related to hypocalcemia is not known. Caution should be exercised when administering Samarium-153 to patients at risk for developing hypocalcemia.
- Concomitant hydration is recommended to promote the urinary excretion of Samarium-153. Appropriate monitoring and consideration of additional supportive treatment should be used in patients with a history of congestive heart failure or renal insufficiency to ensure adequate clearance of drug.

Gastrointestinal

- < 1% of patients experience abdominal pain, diarrhea, nausea/vomiting, and oral candidiasis. GI bleeding was reported in < 1% of patients.

Central nervous system

- < 1% of patients experience cerebrovascular accident, dizziness, paresthesias, spinal cord compression, and stroke.

Cardiovascular

- Adverse reactions have included cardiac arrhythmias, chest pain, hypertension, and hypotension in < 1% of patients. Other cardiovascular adverse reactions include angina, congestive heart failure, sinus bradycardia, and vasodilatation (flushing).

Hematological

- Samarium-153 causes bone marrow suppression. In clinical trials, white blood cell counts and platelet counts decreased to a nadir of approximately 40% to 50% of baseline in 123 (95%) of patients within 3 to 5 weeks after Samarium-153 and tended to return to pretreatment levels by 8 weeks. One percent of patients experienced a CTCAE Grade 4 adverse event. Caution should be exercised in treating cancer patients whose platelet counts are falling or who have other clinical or laboratory findings suggesting disseminated intravascular coagulation (DIC). Because of the potential for bone marrow suppression, beginning 2 weeks after Samarium-153 administration, blood counts should be monitored weekly for at least 8 weeks, or until recovery of adequate bone marrow function.

Renal and Urological

- Special precautions, such as urinary catheterization, should be taken following administration to patients who are incontinent to minimize the risk of radioactive contamination of clothing, bed linen and the patients' environment. Samarium-153 is excreted primarily by the kidneys. In patients with renal dysfunction, the possible risks of administering Samarium-153 should be weighed against the possible benefits.

Carcinogenesis

- Samarium-153 can cause fetal harm when administered to a pregnant woman. Adequate and well controlled studies have not been conducted in animals or pregnant women. Women of childbearing age should have a negative pregnancy test before administration of Samarium-153. If this drug is used during pregnancy, or if a patient becomes pregnant

after taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant soon after receiving Samarium-153. Men and women patients should be advised to use an effective method of contraception after the administration of Samarium-153.

6.3.5 Storage

Storage should be according to the manufacturer's recommendations.

6.3.6 Supply

Commercially available

6.6 Compliance Criteria

Deviations of less than or greater than 20% in the prescribed dose of radiopharmaceuticals is a major deviation (unacceptable).

6.7 Adverse Event Reporting

See Sections 7.5 and 7.6 for reporting requirements.

6.8 Modality Review

The Principal Investigator, Michael Seider, MD, will perform a Quality Assurance Review of all patients who receive or are to receive radiopharmaceuticals in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of treatment data as specified in Section 12.1. The scoring mechanism is: **per protocol; deviation unacceptable; not evaluable for complementary therapy review; or, incomplete complementary therapy**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Seider will perform a Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. Dr. Seider will perform the next reviews for subsequent blocks of 50 cases after the complete data for these cases becomes available at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.0 DRUG THERAPY

All patients on study must complete external beam radiation therapy within 14 days prior to registration. If an Arm 1 patient is receiving chemotherapy or hormonal therapy, therapy schedules may be maintained during protocol treatment.

7.1 Treatment (11/7/08)

7.1.1 Arm 1

Within 1 month of registration, patients on Arm 1 will receive zoledronic acid (Zometa®), 4 mg, once each month. Zoledronic acid will be given monthly for an indefinite period of time and will be discontinued at the discretion of the treating physician. Patients also will take 400 IU of vitamin D and a minimum of 500 mg of calcium orally, daily, starting within 1 month of registration. Patients will take vitamin D and calcium for an indefinite period of time until discontinued at the discretion of the treating physician. Patients will document the daily dose of vitamin D and calcium in a patient diary, and sites will monitor these diaries for completeness in each follow-up visit.

Patients randomized to Arm 1 also may be receiving systemic chemotherapy and/or hormonal therapy. Chemotherapy and/or hormonal therapy should not be changed within 14 days prior to the start of protocol treatment or 14 days after the start of protocol treatment (zoledronic acid).

7.1.2 Arm 2

Within 1 month of registration, patients on Arm 2 will receive zoledronic acid (Zometa®), 4 mg, once each month. Within 6 weeks of registration, patients also will receive a single dose of Strontium-89 OR a single dose of Samarium-153 (see Section 6.1). Patients will receive zoledronic acid prior to and on a different day than the single dose of radiopharmaceutical. Zoledronic acid will be given monthly for an indefinite period of time and will be discontinued at the discretion of the treating physician.

Patients also will take 400 IU of vitamin D and a minimum of 500 mg of calcium orally, daily, starting within 1 month of registration. Patients will take vitamin D and calcium for an indefinite period of time until discontinued at the discretion of the treating physician. Patients will

document the daily dose of vitamin D and calcium in a patient diary, and sites will monitor these diaries for completeness in each follow-up visit.

Patients randomized to Arm 2 also may be receiving hormonal therapy. Hormonal therapy should not be changed within 14 days prior to the start of protocol treatment or 14 days after the start of protocol treatment (zoledronic acid and radiopharmaceutical). **Note:** For Arm 2 patients, chemotherapy must be held 14 days prior to receiving radioisotope and for a minimum of 14 days after radiopharmaceutical administration.

7.1.3 Both Arms

Zoledronic acid will be diluted in 100 mL of solution and administered as an IV infusion over no less than 15 minutes.

Serum creatinine will be measured within seven days prior to each dose of zoledronic acid. The goal dose of zoledronic acid is 4 mg, but the selection of dose is determined based on calculated serum creatinine clearance. See Section 7.5 for details.

Patients exhibiting active dental problems during treatment (documented on the quarterly dental evaluation) must **discontinue** zoledronic acid until the problem is treated, repaired, and/or resolved.

7.2 Zoledronic Acid (Zometa®) [IND exempt for this study]

7.2.1 Formulation

Zometa®, a 3rd generation bisphosphonate, is 2-(imidazol-1-yl-hydroxyethane-1, 1-bisphosphonic acid) in the form of its monohydrate.

7.2.2 Preparation (3/8/07)

Zometa® will be provided in plastic vials containing 4 mg of zoledronic acid in 5 mL concentrate solution for infusion. The Zometa® 4 mg/5 mL concentrate solution is not for direct infusion and has to be further diluted prior to the use. Prior to administration, the 5 mL of the concentrate solution must be diluted with 100 mL calcium-free infusion solution (0.9% sodium chloride solution or 5% glucose solution) so that the total volume infused is 105 mL. The appropriate volume of the reconstituted Zometa® solution is 105 mL. The necessary infusion bags containing 100 mL calcium free 0.9% sodium chloride will be provided. Glass bottles and infusion bags or tubing made from polyvinylchloride (PVC), polypropylene (PP) and polyethylene (PE) are appropriate for use with Zometa®. Zometa® concentrate solution must not be mixed with calcium-containing solutions such as Ringer's solution.

A peripheral or a central intravenous line may be used for the Zometa® infusion. However, the trial-drug infusion may not be mixed with calcium containing infusion solution such as ringer solution and must be given in a single intravenous solution and lined separate from all other drugs. If other medications will be administered through the same IV line, then the line must be flushed with 10 mL of normal saline prior to the administration of these study medications.

7.2.3 Administration

Patients must be evaluated prior to and following the administration of the Zometa® infusion to ensure that they are adequately hydrated. Serum creatinine is to be measured prior to each dose of study drug. The goal dose of Zometa® is 4 mg, but the selection of dose is determined based on calculated serum creatinine clearance. See Section 7.6 for details. Reconstituted Zometa® solutions must be administered in no less than a 15-minute intravenous infusion in a line separate from all other drugs.

7.2.4 Adverse Events

Consult the package insert for comprehensive adverse event information. Based on information from subjects given Zometa® in clinical trials, the potential toxicities include:

Common:

- Hematologic: Anemia
- Neurologic: Headache
- Renal: Renal impairment, hypocalcemia, increased blood urea and/or creatinine
- Gastrointestinal: Nausea/vomiting, anorexia
- Metabolic: Hypophosphatemia
- Ocular: Conjunctivitis
- Allergic: Bone pain, myalgia, arthralgia, fever, flu-like symptoms, fatigue, rigors, malaise

Uncommon:

- Hematologic: Thrombocytopenia, leucopenia

- Cardiac: Hypertension, chest pain, peripheral edema
- Gastrointestinal: Diarrhea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth, weight gain
- Dermatologic: Pruritus, erythematous and macular rash
- Renal: Acute renal failure, hematuria, proteinuria
- Neurologic Dizziness, paresthesia, taste disturbance, anxiety, sleep disturbance, blurred vision
- Allergic: Injection site reactions, hypersensitivity reaction
- Metabolic: Hypomagnesemia
- Other: Increased sweating, muscle cramps, asthenia

Rare

- Cardiac: Bradycardia
- Hematologic: Pancytopenia
- Neurologic: Angioneurotic edema
- Metabolic: Hyperkalemia, hypokalemia, hypernatremia
- Severe, life-threatening allergic reaction

Zometa® should not be given to patients with known allergies to bisphosphonates. Bisphosphonates can cause kidney damage in animals but usually at doses much higher than are given to patients.

In advanced cancer patients receiving, among other anticancer treatments, bisphosphonates, there have been reports of osteonecrosis of the jaw (ONJ). Since many of the patients developing osteonecrosis of the jaw were taking bisphosphonates with chemotherapy, corticosteroids, and radiation, it is not clear if the osteonecrosis is related to the use of bisphosphonates or to these other treatments. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection, including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer chemotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ.

7.2.5 Storage and Stability (7/25/07)

If not used immediately after dilution with infusion media, for microbiological integrity, the final solution must be placed in a refrigerator with a temperature between 2-8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in a refrigerator and end of administration of the infusion must not exceed 24 hours.

7.2.6 Supply

Zometa® will be manufactured and packaged by Novartis and provided to patients on study free of charge. The use of drug in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

7.2.7 Drug Ordering and Accountability (3/8/07) (11/7/08)

Zometa® will be distributed by I.V. Solutions, Inc. I.V. Solutions generally ships drug Monday through Thursday for delivery in 3-5 business days. International shipments may require additional time. RTOG will notify I.V. Solutions to initiate each of these shipments after registration of the patient. Drug shipments may not be immediate if the protocol includes a delay in the initial dosing. Drug will be delivered in time for the patient's first dose. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

The study agent will be sent in two shipments of six (two shipments per year). Each shipment will contain single-use 4 mg vials of Zometa®. **U.S. and Canadian institutions** must submit the Study Agent Shipment Form (SASF) [see Appendix IVI] to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

Note: International sites must receive written approval of submitted LOI forms (http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf) from RTOG Headquarters prior to submitting documents to their Local Ethics Committee for approval.

Approved international institutions must submit the Study Agent Shipment Form and

documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

At the close of the study, sites will return to I.V. Solutions all unused, unopened, non-expired drug, which will be marked clearly with the institution number of the site and the quantity being returned. All other drug can be destroyed or disposed of at the site according to institutional policy. The equivalent of a faxed or mailed memo or email from the responsible party to I.V. Solutions, including the institution number and quantity of study agent destroyed, is required. In a case in which drug expires and requires replacing, the drug can be destroyed on site and reordered through the normal reorder procedure, noting that the re-supply is to replace the destroyed expired drug. . Additional questions about supply and delivery should be directed to:

Angelo Corradino, RPh
Pharmacy Manager
I.V. Solutions, Inc.
162 North Main Street
Old Forge, PA 18518
570-457-9201
Fax 570-457-0465
E-mail: acorradino@choiceonemail.com

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

7.3 Vitamin D

7.3.1 Formulation

Vitamin D analogs are fat-soluble vitamins.

7.3.2 Administration

The patient will take vitamin D, 400 IU (10µg), orally each day.

7.3.3 Adverse Events

Consult the package or package insert for adverse event information. Vitamin D is usually nontoxic; however, the following toxicities may occur:

- Gastrointestinal: Constipation, dyspepsia, nausea, vomiting, diarrhea
- Neurologic: Headaches
- Renal: Renal stones
- Metabolic: Hypercalcemia

7.3.4 Contraindications

Vitamin D should be administered with extreme caution in patients with impaired renal function, renal stones, heart disease, or atherosclerosis.

7.3.5 Storage

Vitamin D should be stored as directed by the commercial supplier.

7.3.6 Supply

Commercially available

7.4 Calcium (11/7/08)

7.4.1 Formulation

Calcium is available in a wide range of preparations.

7.4.2 Administration

A minimum dose of 500 mg of elemental calcium will be administered orally each day. Dose can be adjusted to maintain normal calcium levels and normal calcium homeostasis.

7.4.3 Adverse Events

Consult the package or package insert for adverse event information. Calcium is usually nontoxic; however, the following toxicities may occur:

- Gastrointestinal: Constipation, dyspepsia, nausea, vomiting, diarrhea
- Neurologic: Headaches
- Renal: Kidney stones
- Metabolic: Hypercalcemia

7.4.4 Contraindications

Cardiac glycosides and calcium are synergistic, and arrhythmia may occur if these drugs are given together.

7.4.5 Drug Interactions

Tetracycline and calcium should not be given at the same time, as calcium complexes tetracycline antibiotics, rendering them inactive.

7.4.6 Storage

Calcium should be stored as directed by the commercial supplier.

7.4.7 Supply

Commercially available

7.5 Dose Modifications: Zoledronic Acid (11/7/08)

Serum creatinine will be measured within 7 days prior to each dose of study drug. The goal dose of zoledronic acid (Zometa®) is 4 mg, but the selection of dose is determined based on calculated serum creatinine clearance (see parameters below) estimated by Cockcroft-Gault formula:

$$\text{CrCl male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{sCR}) \times (72)]}$$

$$\text{CrCl female} = 0.85 \times (\text{CrCl male})$$

The laboratory result must be available prior to administration of the dose of zoledronic acid. Serum creatinine monitoring should be done in accordance with clinical standard of care, which must not be less frequent than the approved Zometa® label recommendation of assessing serum creatinine prior to each administration.

Dose Determination Based on Calculated Creatinine Clearance	
Creatinine Clearance	Zoledronic Acid Dose
> 60 ml/min	4 mg
50-60 ml/min	3.5 mg
40-49 ml/min	3.3 mg
30-39 ml/min	3 mg

7.5.1 Deciding Whether to Treat After the First Zoledronic Acid (Zometa®) Dose

Serum creatinine will be measured within 7 days prior to each dose of zoledronic acid. If base line serum creatinine was < 1.4 mg/dl at study entry, than an increase of 0.5 mg/dl requires a delay in treatment until the patient's serum creatinine returns to no higher than 10% above the base line value. If the base line serum creatinine was > 1.4 at study entry, then an increase of 1.0 mg/dl requires a delay in treatment until the patient's serum creatinine returns to no higher than 10% above the base line value. For patients who require a delay, the delay will be a 1 month delay such that if a patient has serum creatinine changes that require a delay, the dose will be skipped for that particular 1 month period of time and assessment will occur again at the regular scheduled subsequent 1 month visit. Serum creatinine will be checked within a week of that next dosing time and parameters listed above will be followed.

7.5.2 Delay or Discontinuation of Other Therapies

If Arm 2 patients fail to receive a single dose of radiopharmaceutical or if patients on either Arm 1 or Arm 2 fail to take vitamin D or calcium supplements, they will continue to receive zoledronic acid per protocol.

Patients exhibiting active dental problems during treatment (documented on the quarterly dental evaluation) must **discontinue** zoledronic acid until the problem is treated, repaired, and/or resolved.

7.6 Modality Review

The Medical Oncology Co-Chair, Corey Langer, MD, will perform a Quality Assurance Review of all patients who receive or are to receive zoledronic acid in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of treatment data as specified in Section 12.1. The scoring mechanism is: **per protocol; variation, acceptable; deviation unacceptable; not evaluable for complementary therapy review; or, incomplete complementary therapy.** A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Dr. Langer will perform a Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. Dr. Langer will perform the next reviews for

subsequent blocks of 50 cases after the complete data for these cases becomes available at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.7 Adverse Events (11/7/08)

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA, version 6.0, for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

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

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

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

7.7.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. January 2005; <http://ctep.cancer.gov/reporting/adeers.html>]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.8 also must be reported via AdEERS.

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

7.7.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

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

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

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- The following **medically significant events** have been identified as requiring reporting on this protocol as SAEs:
 1. Osteonecrosis of the jaw (severity grades 1-5);
 2. Osteomyelitis (of any bone) [severity grades 2-5].

Regardless of grade, sites must report all osteonecrosis of the jaw and all osteomyelitis of any bone via AdEERS.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

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

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

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

7.7.3

Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at <http://ctep.cancer.gov/forms/index.html>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and **must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.8 AdEERS Expedited Reporting Requirements

Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days¹ of the Last Dose of the Investigational Agent Zometa® in this Study (Arm 1) and Zometa® plus radiopharmaceutical (Arm 2)

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

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

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

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

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

- Expedited AE reporting timelines defined:
 - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - "10 calendar days" – A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a non-CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

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

In IND-exempt studies, such as this one, RTOG will provide Novartis Pharmaceuticals with a copy of all SAE reports by FAX within 24 hours of receipt. These reports will be completed via AdEERS as detailed above and will include serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse events. See Section 7.7.2 for special reporting requirements for this study.

NOTE: All adverse events will be reported by the site to the site IRB. All unexpected deaths during treatment or within 30 days following completion of protocol therapy will be reported within 5 working days.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.1 All patients on study must complete external beam radiation therapy within 14 days prior to registration.

Note:

- If an Arm 2 patient needs to restart radiation therapy (e.g., for lung metastasis; NO treatment of bone metastases), it is strongly recommended that radiotherapy should not commence for a **minimum** of 14 days after receiving a radiopharmaceutical;
- For Arm 2 patients: If the patient is receiving chemotherapy, the therapy should not be given within 14 days of and for a **minimum** of 14 days after receiving a radiopharmaceutical;
- For Arm 2 patients: If the patient is receiving hormonal therapy, the therapy should not be changed within 14 days prior to and for a minimum of 14 days after receiving a radiopharmaceutical;
- If an Arm 1 patient is receiving chemotherapy or hormonal therapy, therapy schedules maybe maintained during protocol treatment.

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

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Dental Safety

After study entry, any patient report of the following symptoms at interim visits will require a follow-up examination by a qualified dental professional (dental hygienist or dentist) to rule out osteonecrosis of the jaw (ONJ) prior to further doses of zoledronic acid:

- Exposed bone in the oral cavity;
- Rough area on the jawbone;
- "Heavy jaw", a dull aching sensation;
- Numbness or tingling of the jaw;
- Loosening of teeth;
- Tooth pain;
- Sudden change in the health of periodontal or mucosal tissue;
- Failure of oral mucosa to heal;
- Undiagnosed oral pain;
- Soft tissue swelling, drainage, or infection.

If exposed bone is observed on dental examination, the patient will be referred to an oral surgeon for a panoramic x-ray, diagnosis, and treatment. If a diagnosis of ONJ is made, zoledronic acid will be discontinued, and further treatment will be at the discretion of the treating physician.

11.3 Criteria for Removal from Protocol Treatment (3/8/07)

11.3.1 Unacceptable adverse event(s) to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flow sheet;

11.3.2 The investigator or treating physician may withdraw the patient from protocol treatment if it is felt to be in the patient's best interest — Reasons for withdrawing the patient must be clearly documented on the appropriate case report form/flow sheet.

11.3.3 Patients discontinuing treatment should continue to be followed for study endpoints.

11.4 Quality of Life Assessments

11.4.1 *The Functional Assessment of Cancer Therapy – General (FACT-G)*

The FACT-G is a commonly used tool measuring general quality of life across 4 scales: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items). It has been written at the 4th grade reading level, and

patients can complete the FACT-G in 5-10 minutes. The FACT has been translated into 26 languages, and translations are accessible at the FACIT web site, <http://www.facit.org/translation/licensure.aspx>.

11.4.2 The Brief Pain Inventory (BPI)

The BPI asks patients to rate their pain for the last week on 0-10 scales. Patients also are asked to rate how their pain interferes with their quality of life (QOL). Patients also are asked to estimate the pain relief they receive from their pain treatment. The patient can complete the BPI in approximately 5 minutes. The BPI has been validated in 12 languages. Translations can be accessed at <http://www.mdanderson.org/departments/prg/>; click on “symptom assessment tools”. If a translation is used, the site must transcribe the data to the appropriate RTOG data form and attach the patient’s original.

11.4.3 The EuroQol (EQ-5D)

The EQ-5D is a two-part questionnaire that the patient can complete in approximately 5 minutes. Note: The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at <http://www.euroqol.org/>. The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the Health Utility Measurement (HP) form.

12.0 DATA COLLECTION

Data should be submitted to:

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

***If a data form is available for web entry, it must be submitted electronically.**

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

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1)	2 weeks post-registration
Functional Assessment of Cancer Therapy (FACT-G) [PQ] Brief Pain Inventory (BPI) [QL] EuroQol (EQ-5D) [HP]	Baseline (prior to any treatment), then at 1, 3, 6, and 12 months from start of treatment
Treatment Form (TF)	Monthly for 1 year or until patient discontinues monthly zoledronic acid
Follow-up Form (F1)	At 1, 3, 6, and 12 months from start of treatment then beginning year 2, every 6 months for the patient’s lifetime
Adverse Event Form (AE)	At 1, 3, 6, and 12 months from start of treatment and/or as needed when patient is assessed for treatment adverse events

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Time to development of a malignant skeletal related event (SRE), defined as a pathological bone fracture, spinal cord compression, surgery to bone or radiation to bone

13.1.2 Secondary Endpoints

13.1.2.1 SRE rate at one year;

13.1.2.2 Overall survival;

13.1.2.3 Changes in Quality of Life using The Functional Assessment of Cancer Therapy–General (FACT-G);

13.1.2.4 Changes in pain control using the Brief Pain Inventory (BPI);

13.1.2.5 Evaluate the utility and cost effectiveness, as measured by The EuroQol-5 Dimension (EQ-5D), of the use of radiopharmaceuticals and bisphosphonates;

13.2 Sample Size

13.2.1 Stratification and Randomization

Patients will be stratified before randomization according to primary disease site (prostate vs. breast vs. lung) and number of bone metastases (≤ 2 vs. > 2). The treatment allocation scheme described by Zelen⁵⁶ will be used because it balances patient factors other than institution. Patients will be randomized to receive bisphosphonates \pm a radionuclide [Strontium-89 (Sr-89) or Samarium-153 (Sm-153)].

13.2.2 Sample Size Derivation

The sample size calculation will address the specific primary hypothesis that the addition of a radionuclide [Sr-89 or Sm-153] to bisphosphonates for patients with asymptomatic or stable symptomatic bone metastasis will have a clinically meaningful different median time to progression of malignant skeletal related events (SREs) as compared to patients receiving bisphosphonates alone. The Zometa® study⁵⁷ indicated the median time to the first SRE to be 14.8 months (*yearly SRE hazard rate* = 0.5620) for prostate and 12 months (*yearly SRE hazard rate* = 0.6932) for breast cancer patients receiving bisphosphonates. Rosen et al.²⁰ demonstrated the median time to the first SRE to be 5.6 months (*yearly SRE hazard rate* = 1.4853) for lung cancer patients receiving bisphosphonates. We expect the distribution to be 40% from prostate, 40% from breast, and 20% from lung cancer. The median time to first SRE for the control arm is estimated by weighting the yearly SRE hazard rate by the proportion of disease site expected to be included in the study as such:

$$\lambda_{\text{SRE, C}} = 0.4\lambda_{\text{SRE, C, Prostate}} + 0.4\lambda_{\text{SRE, C, Breast}} + 0.2\lambda_{\text{SRE, C, Lung}}$$

The null hypothesis (H_0) of this test is that the hazard rate of the bisphosphonates only arm (*control*, $\lambda_{\text{SRE,C}}$) is the same as the hazard rate of the bisphosphonates + Sr-89 or Sm-153 arm (*experimental*, $\lambda_{\text{SRE,E}}$). The alternative hypothesis (H_A) is that the hazard rate of the control arm is different than the experimental arm.

$$H_0: \delta_{\text{SRE}} = 0 \quad \text{vs.} \quad H_A: \delta_{\text{SRE}} \neq \delta_1$$

where $\delta_1 = -\ln(\lambda_{\text{SRE,E}}/\lambda_{\text{SRE,C}})$. Assuming an exponential distribution, the weighted yearly SRE hazard rate for patients treated with bisphosphonates only is 0.7991. This translates to a median time to SRE of 10.4 months. The study is designed to show a 33% relative reduction in the yearly SRE hazard rate, i.e., a median time to SRE of 15.6 months (yearly SRE hazard rate of 0.5328). This translates to an absolute improvement of 5.2 months in the median time to SREs. The following assumptions and parameters were used to determine the required number of SREs and patients for the primary endpoint:

- The times free of SREs are exponentially distributed in the treatment arms;
- The yearly SRE hazard rate on the bisphosphonates alone arm is 0.7991 (weighted average of yearly SRE hazard rates by disease site strata);
- The yearly SRE hazard rate on the bisphosphonates and of a radionuclide arm is 0.5328 (weighted average of yearly SRE hazard rates by disease site strata);
- A design effect of 33%, that is, a relative reduction in the yearly SRE hazard rate of at least 33% in the bisphosphonates and radionuclide arm, from 0.7991 to 0.5328 (or $\delta_1 = -\ln(\lambda_E/\lambda_C) = 0.405$);
- Two-sided log-rank test at $\alpha = 0.05$;
- Statistical power of 90%;
- Four years of accrual with additional follow-up of 1 year after the last patient entered on the study;

- One interim analysis and a final analysis for efficacy using Haybittle-Peto boundaries.⁵⁸

Using a log-rank test and the same number of patients in each treatment arm, 257 SREs are required with a total of 316 patients. Guarding against an ineligible rate up to 10%, **the final targeted accrual for this study will be 352 cases.**

13.2.3 Power Calculations for Secondary Endpoints

13.2.3.1 One-year SRE rate

Under the assumptions of Section 13.2.2 relating to the yearly hazard rate of SRE, the one-year failure rates are 55% in the control arm and 41% in the experimental arm. The power of detecting such a difference with a two-sided Fisher's exact test⁵⁹ with alpha 0.05 is 66%

13.2.3.2 Overall Survival

The clinical experience from Rosen et al.²⁰ showed a median survival time (yearly death rate) for prostate, breast, and lung cancer patients is approximately 36 months (0.2311), 48 months (0.1733) and 6 months (1.3.863), respectively. We expect the distribution to be 40% from prostate, 40% from breast, and 20% from lung cancer. The median survival time for the control arm is estimated by weighting the yearly death rate by the proportion of disease site expected to be included in the study as such:

$$\lambda_{OS, C} = 0.4\lambda_{OS, C, Prostate} + 0.4 \lambda_{OS, C, Breast} + 0.2 \lambda_{OS, C, Lung}$$

The null hypothesis (H_0) of this test is that the hazard rate of the bisphosphonates only arm (control, $\lambda_{OS,C}$) is the same as the hazard rate of the bisphosphonates + Sr-89 or Sm-153 arm (experimental, $\lambda_{OS,E}$). The alternative hypothesis (H_A) is that the hazard rate of the control arm is different than the experimental arm.

$$H_0: \delta_{OS} = 0 \quad \text{vs.} \quad H_A: \delta_{OS} \neq \delta_1$$

where $\delta_1 = -\ln(\lambda_{OS,E}/\lambda_{OS,C})$. Assuming the disease site distribution is 40%, 40%, and 20% from prostate, breast, and lung cancer populations, respectively, the weighted yearly death rate for patients treated with bisphosphonates only is 0.4390. This translates to a median overall survival time of 18.9 months assuming an exponential distribution. The statistical power to detect a relative difference of 33% in the yearly death rate is 70% using a two-sided log-rank test at a 0.05 level of significance, and the power to detect a 50% difference in yearly death rate is 87%.

13.2.3.3 Quality of Life

General Quality of Life (QOL) will be measured using the Functional Assessment of Cancer Therapy-General (FACT-G, version 4.0).⁴⁸ Pain will be measured using the Brief Pain Inventory (BPI) tool.⁴⁹⁻⁵⁰ Health Related Quality of Life (HRQOL) and health utility will be measured using the EuroQol (EQ-5D).⁵¹⁻⁵² These tools will be administered pre-treatment and at 4 weeks and at 3, 6, and 12 months.

13.3 Patient Accrual

Based on patient accrual in previous RTOG randomized studies, there will be relatively few entries during the initial six months while institutions are obtaining IRB approval. The RTOG Data Monitoring Committee (DMC) will begin evaluating patient accrual semi-annually following this anticipated quiet period. The patient accrual is projected to be 7.3 cases per month (or 88 cases per year). We expect to complete the accrual in 4 years. The total duration of the study is expected to be 5 years from the time the first patient is entered to the final analysis. If the average monthly accrual rate between 12 and 18 months after activation is below 2 cases per month, the study will be re-evaluated for its feasibility. If the study is continued after 18 months with fewer than 2 cases per month and then at 24 months after study activation, if the average monthly accrual between 19 and 24 months is less than 2 patients per month, i.e., less than 20% of the projected 7.2 cases per month, the study statistician will recommend to the RTOG DMC that the study be terminated.

13.4 Analysis Plan

All eligible patients randomized will be included in the comparison of treatment arms (intent-to-treat analysis).

13.4.1 Primary Endpoint

The primary endpoint is median time to development of a Skeletal Related Event (SRE). The time of failure will be measured from the date of randomization to the date of a documented

SRE as defined in Sections 1.4, 2.1, and Appendix II. The median time to a SRE will be estimated by the Kaplan-Meier method.⁶⁰ The null and alternative hypotheses are:

$$H_0: \delta_{SRE} = 0 \quad \text{vs.} \quad H_A: \delta_{SRE} \neq 0.405$$

where $\delta_1 = -\ln(\lambda_{SRE,E} / \lambda_{SRE,C})$. A stratified log-rank test will be used to test the primary hypothesis⁶¹ with a significance level of 0.0498 at the final analysis. In addition, unadjusted and adjusted hazard ratios and the respective 95% confidence intervals will be computed using the Cox proportional hazards regression model.⁶² Primary disease site, number of bone metastases and other baseline factors, as appropriate, will be adjusted in this analysis.

13.4.2 Secondary Endpoints

13.4.2.1 One-year SRE rate

The one-year SRE rates will be calculated from a 2x2 contingency table pictured below:

	Number of cases with an SRE at one year	Number of cases without an SRE at one year
Control arm	a	c
Experimental arm	b	d

The difference in rates will be tested using a two-sided Fisher's exact test with significance level of 0.05.

13.4.2.2 Overall Survival

We assume that the distributions of deaths over time are exponentially distributed. The time of failure will be measured from the date of randomization to the date of documented death due to any cause. The median survival times will be estimated by the Kaplan-Meier method. The null and alternative hypotheses are:

$$H_0: \delta = 0 \quad \text{vs.} \quad H_A: \delta \neq 0.401$$

where $\delta_1 = -\ln(\lambda_{OS,E} / \lambda_{OS,C})$. A conservative and clinically meaningful difference is 0.401, which is derived from a 33% relative difference in the yearly failure rate of the bisphosphonates only arm. A stratified log-rank test will be used to test the null hypothesis with a significance level of 0.05 at the final analysis. In addition, unadjusted and adjusted hazard ratios and the respective 95% confidence intervals will be computed using the Cox proportional hazards regression model. Primary disease site, number of bone metastases and other baseline factors, as appropriate, will be adjusted in this analysis.

13.4.2.3 Quality of Life Measured by the FACT-G and Pain Control Measured by the BPI

The primary patient-reported endpoint for the FACT-G and BPI will be differences between arms in the mean FACT-G scores (total and four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being) and mean BPI score, respectively, using all assessments as described in Section 13.2.3.2 from baseline (i.e., pre-treatment) to 12 months from start of protocol treatment for each patient. Longitudinal data analysis will be performed to describe the change trend of the scores over time across the two treatments using an appropriate model, such as the hierarchical formulation of the linear mixed model.⁶³ The response will be the change of measurement from baseline for each domain. A Bonferroni-adjusted significance level will be used to maintain the overall significance level for the comparison of the four subscales and total score for the FACT-G. To test the null hypothesis that the responses are the same across the treatment arms, a Bonferroni-adjusted $\alpha = 0.01 = 0.05/5$ will be used. The model will include the stratification variables, primary disease site, and number of bone metastases as well as any other baseline factors as appropriate. There will be an assessment as to whether the missing observations are random or informative. The missing observations can be categorized as: Missing Completely at Random (MCAR) when the probability of a missing observation is independent of the observed and missing data, Missing at Random (MAR) when the probability of a missing observation may depend on the observed data but is conditionally independent of the missing data given the observed data and Missing Not at Random (MNAR) when the probability of a missing observation is not conditionally used to determine if the data are MCAR vs. MAR. If the MCAR is suspected regardless of the amount of missing data, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then a multiple imputation method⁶⁴ will be applied to

impute the missing data if greater than 5% of the data are missing otherwise, complete case methods will be done. Patients that die and do not have an assessment will be imputed using the worst FACT-G or BPI score for the patient as the most conservative imputation approach. If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR must be addressed by an explicit model for the missing data mechanism⁶⁵ and a multiple imputation method will be applied. All results from the imputed analysis using the multiple imputation method will be compared to the complete case analysis results to assess any potential biases. A summary of the potential pathways are shown below:

Missing Data Mechanism	Percent Data Missing	
	≤ 5%	> 5%
MCAR	Complete Case	Complete Case
MAR	Complete Case	Multiple Imputation
MNAR	Multiple Imputation after satisfying MAR	Multiple Imputation after satisfying MAR

An Area Under the Curve (AUC) analysis will also be done using all FACT-G subscales and total score and BPI assessments from baseline to 12 months from start of protocol treatment for each patient. For the BPI, a two-sample t-test with a two-sided $\alpha = 0.05$ will be used to test the null hypothesis that the mean AUC of the bisphosphonates only arm is the same as the bisphosphonates + Sr-89 or Sm-153 arm versus the alternative that the bisphosphonates only arm is different than the bisphosphonates + Sr-89 or Sm-153 arm. For FACT-G comparison, a two-sample t-test with a two-sided Bonferroni-adjusted $\alpha = 0.01 = 0.05/5$ will be used to control the overall type 1 error rate for testing multiple domains.

13.4.2.4

Cost-Utility and Cost-effectiveness Measured by the EQ-5D

The primary patient-reported endpoint for the EQ-5D will be differences between arms in the quality adjusted survival and cost-utility outcomes using all assessments as described in section 13.2.3.2 from baseline (i.e., pre-treatment) to 12 months from start of protocol treatment for each patient. The EQ-5D will be used to generate health utilities, which will then be used in deriving quality adjusted survivals. The utility scores lie between 0 “Worst health state” and 1 “Best health state”. It will provide two utility scores; one of which is from 5-item index score and other from visual analogue scale (VAS), and both will be used in generating separate quality adjusted survivals. Quality adjusted survival will be computed using the weighted sum of different time in different health states added up to a total quality-adjusted survival time where $U = \sum_{i=1}^K q_i s_i$

$$U = \sum_{i=1}^K q_i s_i$$

The log-rank test will be used to compare quality-adjusted survivals between the treatment arms.

13.4.3 Significance Testing for Early Termination and Reporting of Efficacy

A group sequential test with one planned interim analysis and a final analysis will be performed for efficacy of the experimental treatment using Haybittle-Peto boundaries. The null and alternative hypotheses of the primary endpoint are:

$$H_0: \delta_{SRE} = 0 \quad \text{vs.} \quad H_A: \delta_{SRE} \neq 0.405$$

where $\delta_1 = -\ln(\lambda_{SRE,E} / \lambda_{SRE,C})$. At the planned interim analysis, the p-value from the stratified log-rank test assessing treatment efficacy will be compared with the nominal significance level (α_n). The boundary for early stopping for efficacy will be computed based on the observed number of skeletal related events according to the Haybittle-Peto boundaries. If the computed p-value is less than or equal to the nominal significance level boundary (α_{n1}), then we will stop the trial and conclude that the median SRE rate of the bisphosphonates + Sr-89 or Sm-153 arm

is different than the bisphosphonates only arm (reject the null hypothesis, H_0). Otherwise, we will continue the trial.

Nominal Significance Levels (α_n) for the Interim Analysis

Time of Interim Analysis	Nominal Significance Level
Number of Skeletal Related Events	Reject H_0 if $p\text{-value} \leq \alpha_{n1}$
128	0.001

The responsible statistician will recommend to the RTOG DMC that the randomization be discontinued, if applicable, and the study be considered for early publication. Before making such a recommendation, the accrual rate, safety of the treatments, and the importance of the study are also taken into consideration with the p-value. The RTOG DMC will then make a recommendation about the trial to the RTOG Group Chair.

13.4.4 Interim Analysis of Accrual and Adverse Event Data

Interim reports will be prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The major components of this report are:

- The patient accrual rate with a projected completion date for the accrual phase;
- Accrual by institution;
- The distribution of pretreatment characteristics;
- Compliance with the submission of baseline quality of life questionnaires;
- The frequency and severity of the adverse events.

The study statistician will report any problems identified to the study chairs, RTOG CCOP/Symptom Management committee, the RTOG DMC, and if appropriate, to the RTOG Executive Committee.

In addition, this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.4.5 Reporting the Initial Treatment Analysis

The primary hypothesis of this study is to determine if there is a difference in the median time to SREs of patients receiving bisphosphonates + Sr-89 or Sm-153 compared to that of patients receiving bisphosphonates alone. The analysis reporting the treatment results will be carried out after 257 skeletal related events have been observed, unless the criteria for early stopping are met. The difference between the median time to a SRE of the control (bisphosphonates only) and the experimental arm (bisphosphonates + Sr-89 or Sm-153) will be tested using the stratified log-rank test at a significance level of 0.0498 given that the one interim analysis is carried out as described in Section 13.4.3. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; safety treatments; compliance with submission of QOL questionnaires; and observed results with respect to the primary and secondary endpoints. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). The Cox proportional hazard model including the stratification variables, primary disease site and number of bone metastases, will be used for exploratory analyses of treatment comparisons. Also, where feasible, treatment comparisons with respect to all endpoints will be compared within gender and ethnic/racial categories.

13.4.6 Inclusion of Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of men will be examined in the interim analyses. Based on accrual statistics from RTOG 97-14, the projected accrual by gender and race/ethnicity is shown below.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	11	7	18
Not Hispanic or Latino	169	165	334
Ethnic Category: Total of all subjects*	180	172	352
	Gender		
Racial Category	Females	Males	Total
American Indian or Alaskan Native	2	2	4
Asian	2	2	4
Black or African American	30	36	66
Native Hawaiian or other Pacific Islander	2	2	4
White	144	130	274
Racial Category: Total of all subjects*	180	172	352

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APPENDIX I

RTOG 0517

Informed Consent Template for Cancer Treatment Trials (English Language)

Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have lung, breast, or prostate cancer that has spread to your bone.

Why is this study being done?

When cancer spreads to the bone, it can cause bone pain and fractures (breaks) and/or pressure on the spinal cord.

The purpose of this study is to compare the effects, good and/or bad, of a two different combinations of drugs to see which is better. One combination includes zoledronic acid (Zometa®), vitamin D and a calcium supplement. Zoledronic acid is a drug given through the vein to strengthen bones. The other combination includes zoledronic acid, vitamin D, and a calcium supplement plus one of two types of a radiopharmaceutical. A radiopharmaceutical is a radioactive drug given through the vein to attack cancer in the bone. In this study, you will get one of the combinations of drugs, not both.

How many people will take part in the study?

About 352 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. In addition, you should talk with your dentist about taking part in this study.

- A physical exam
- You will be asked about your ability to carry out your daily activities.
- Blood tests for red and white blood cell levels, kidney function, and liver function
- A bone scan, a type of x-ray to verify that cancer has spread to your bones
- For women who can have children, a pregnancy test

In addition, if the study doctor feels it is in your best interests, your teeth, gums, and chewing ability will be evaluated.

Before treatment

Patients who receive a single dose of a radiopharmaceutical (see “group 2” below) will need the following tests two weeks before receiving the radiopharmaceutical:

- Blood tests for red and white blood cell levels
- Blood test for kidney function

During the Study (3/8/07) (7/25/07) (11/7/08)

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. These tests are part of regular cancer care.

- Blood tests for red and white blood cell levels weekly for 8 weeks
- Blood test for kidney function once a month before you receive zoledronic acid

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your study doctor can choose the group in which you are placed. You will have an equal chance of being placed in any group.

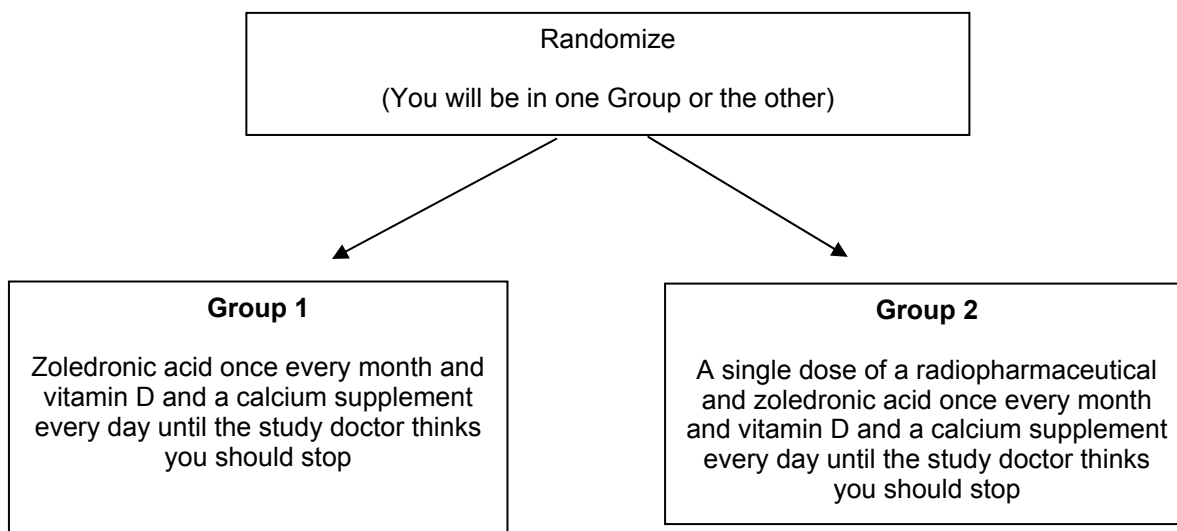
If you are in group 1 (often called “Arm A”), you will receive 4 mg of zoledronic acid (Zometa®) through your vein once a month until the study doctor thinks it is in your best interest to stop. Each infusion takes about 15 minutes. You also will take 400 IU of vitamin D (1 pill) and at least 500 mg of calcium (1 pill) by mouth daily until the study doctor thinks it is in your best interest to stop.

If you are in group 2 (often called “Arm B”), you will receive a single dose of a radiopharmaceutical, either 4 mCi of Strontium-89 or 1mCi/kg of Samarium-153, through your vein. The study doctor will talk with you about which radiopharmaceutical you will receive. Receiving the radiopharmaceutical takes about 5 minutes. In addition, you will receive 4 mg of zoledronic acid (Zometa®) through your vein once a month until the study doctor thinks it is in your best interest to stop. Each infusion takes about 15 minutes. You also will take 400 IU of vitamin D (1 pill) and at least 500 mg of calcium (1 pill) by mouth daily until the study doctor thinks it is in your best interest to stop.

You will be seen once a month as long as you take zoledronic acid, vitamin D, and calcium. If you stop taking zoledronic acid, vitamin D, and calcium, you will be seen in follow-up visits a minimum of every 6 months for your lifetime.

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

For Both Group 1 and Group 2:

You will be asked to take zoledronic acid, vitamin D, and a calcium supplement until the study doctor thinks it is in your best interest to stop. You will be seen once a month as long as you take zoledronic acid, vitamin D, and calcium. If you stop taking zoledronic acid, vitamin D, and calcium, you will be seen in follow-up visits a minimum of every 6 months for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the zoledronic acid or radiopharmaceuticals can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the zoledronic acid or radiopharmaceutical. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks Related to Zoledronic Acid (Zometa®) [3/8/07]

You should not have dental surgery (teeth pulled or implanted) while you are receiving Zometa®, as it may delay recovery from that surgery.

Likely

- Low red blood cell counts, which may cause tiredness, shortness of breath, and/or fatigue
- Headaches
- Nausea and/or vomiting
- Loss of appetite leading to weight loss
- Inflammation of the white of the eye, which may require eye drops to ease discomfort
- Tiredness
- Low levels of phosphates in the blood, which may cause muscle weakness
- Low calcium levels in the blood, which could result in numbness or tingling around the mouth and in the hands, and feet as well as muscle spasms in the face, hands, and feet
- Flu-like symptoms, including fever, flushing, chills, and joint and muscle aches, which are generally seen after the first zoledronic acid treatment
- Decreased kidney function

Less Likely

- Dizziness and/or blurred vision
- Weakness
- Increased sweating
- Redness of the skin and/or itching

- Difficulty sleeping
- Feeling anxious
- Irritation inside the mouth
- Change in taste
- Constipation and/or stomach pain
- Upset stomach
- Diarrhea
- Dry mouth
- Weight gain
- Tingling in the fingers and toes
- Swelling of hands and feet
- Low platelets, which help the blood clot
- Low white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding
- A reaction at the injection site, which may include pain, redness, tenderness, swelling, and/or bruising
- Allergic reactions, which may include itching, flushing, sweating, rash, and/or shortness of breath
- High blood pressure
- Chest pain
- Decreased magnesium in the blood, which can cause tiredness or muscle cramps
- Sudden kidney failure, which could be permanent

Rare, but serious

- Decreased heart rate
- Decreased amounts of blood cells, which may cause tiredness, shortness of breath, and/or fatigue and may require treatment
- Swelling of skin, the lining of the mouth and throat, and/or organs, which may result in discoloration of the skin, joint pain and/or fever and which may require treatment
- Changes in electrolytes (body salts), which usually causes no symptoms but can sometimes cause tiredness, muscle weakness, cramping, rigidity, irregular heart beat, or seizures that could become severe and possibly life threatening. This could require hospitalization and/or treatment through your vein.
- Severe allergic reactions, which would require treatment and which could be life-threatening
- Permanent damage to the jawbone, which may be painful and may require surgery to remove damaged areas
If you have dental pain or dental problems, you must tell the study doctor immediately.

Risks of Zoledronic Acid Reported in Other Studies

In a recent study in post-menopausal women with osteoporosis, a small number of patients treated with zoledronic acid experienced an irregular heartbeat called atrial fibrillation. More patients who received zoledronic acid experienced this kind of irregular heartbeat than patients who did not receive zoledronic acid. This irregular heartbeat has not been observed to date in studies of zoledronic acid in cancer patients. Atrial fibrillation is a common condition that can be treated. More research is needed before the importance of this finding becomes clear.

Risks and side effects related to the Radiopharmaceuticals

Radiopharmaceuticals are **radioactive**, and **some caution is necessary**. For about 12 hours after you receive the radiopharmaceutical, radioactivity will be present in your urine. Whenever possible, you should use a toilet rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely, and you should wash your hands thoroughly. If blood or urine gets onto your clothing or bedding, the clothing and bedding should be washed separately from other items.

Strontium-89 Chloride

Likely

- Decreased white blood cell counts, which may increase the risk of infection, decreased healing, and/or bleeding
- Decreased platelets, which help the blood clot

Less Likely

- Bone pain that usually goes away in 48 hours

- Chills and/or fever
- Flushing

Rare but serious

- Acute leukemia (cancer of the blood or blood-forming organs)

Samarium-153

Likely

- Decreased blood counts, which can lead to tiredness, shortness of breath, infection, or easy bruising and/or bleeding
- Nausea and/or vomiting
- Inflamed lymph nodes (small bodies in the lymphatic vessels that filter bacteria)
- Increased or decreased blood pressure
- Irregular heart rhythm

Less Likely

- Hair loss
- Stomach pain
- Diarrhea
- Mouth sores
- Itching
- Rash
- Dizziness
- Numbness and/or tingling
- Muscle weakness
- Cough
- Flushing
- Fever and/or chills
- Chest pain

Rare but serious

- Bleeding in the bowel
- Bleeding in the eye
- Stroke (damage to the brain due to interrupted blood flow or bleeding into the brain)

Risks Related to Vitamin D and Calcium Supplements

Taking the dose of vitamin D and calcium in this study is generally safe, but the following side effects have been reported:

Likely

- Constipation

Less Likely

- Headaches
- Stomach irritation
- Nausea and/or vomiting
- Diarrhea
- Kidney stones

Less Likely but Serious

- Too much calcium in the blood, which could result in sleepiness, weakness, and if severe, could cause coma (a non-responsive, sleep-like condition resulting from injury to the brain)

Risks and side effects related to having blood drawn for routine laboratory tests

Likely

- Minor pain or discomfort

Less Likely

- Bruising
- Infection

Other Medicine

You should talk to the study doctor about the other medicine (prescription or over-the counter drugs, herbal and/or nutritional supplements) you are taking because some drugs may increase the risk of developing side effects from zoledronic acid or calcium.

- If you take water pills, such as furosemide, while you are receiving zoledronic acid, you may experience low potassium.
- If you take antibiotics, such as gentamicin, while you are receiving zoledronic acid, you may experience low calcium.
- You should not take calcium and tetracycline antibiotics at the same time because calcium will make the tetracycline less effective.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope that zoledronic acid and/or radiopharmaceuticals will delay bone pain, fractures, and/or pressure on the spinal cord, there is no proof of this yet. We do know that the information from this study will help researchers learn more about zoledronic acid and radiopharmaceuticals as a treatment for cancer that has spread to the bone. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for bone pain, fractures, and/or pressure on the spinal cord without being in a study
- Taking part in another study
- Getting no treatment for bone pain, fractures, and/or pressure on the spinal cord

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (11/7/08)

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Novartis, the manufacturer of Zometa® (zoledronic acid)
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials [for CTSU participants only]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Novartis is supplying Zometa® (zoledronic acid) at no cost to you. However, you or your health plan may need to pay for costs of the supplies to administer the drug and for the personnel who give you the zoledronic acid. In addition, your doctor/hospital may supply the vitamin D and calcium supplements at no cost to you.

Talk to your doctor/institution about receiving the vitamin D and calcium at no cost and for assistance in checking with your insurance company for coverage of study examinations and procedures.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your names or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research.

You can say "yes" or "no" to the following study. Below, please mark your choice.

Quality of Life Study (11/7/08)

We want to know your view of how your life has been affected by cancer and its treatment. This "quality of life" study looks at how you are feeling physically and emotionally during your cancer treatment. It looks at how you are able to carry out your day-to-day activities. In addition, you will be asked to rate your pain for each week on a 0-10 scale and to rate how your pain interferes with your quality of life.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer and the side effects of cancer treatment.

You will be asked to complete 3 questionnaires on your first visit and at 1, 3, 6, and 12 months from the start of treatment. It takes about 5-10 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the three questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the three Quality of Life Questionnaires.

YES

NO

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II (3/8/07) (7/25/07)

STUDY PARAMETER TABLE

Assessments	Pre-Treatment				During Treatment**					
	Within 2 wks prior to registration	Within 4 wks prior to registration	Within 8 wks prior to registration	ARM 2 patients Within 2 wks prior to treatment	Weekly for 8 weeks	Within 7 days prior to each dose of zoledronic acid	At 4 weeks	Monthly	Every 3 months	At 3, 6, and 12 months from the start of treatment
History/physical			X							
Bone scan		X								
Performance status										
CBC w/ diff & ANC	X			X	X					
Platelets; Hgb	X				X					
Serum creatinine	X			X		X				
Total bilirubin	X									
Pregnancy test (if applicable)	X									
Dental Eval			X						X	
FACT-G	X						X			X
BPI	X						X			X
EQ-5D	X						X			X
Adverse event evaluation*								X		

*And as needed based on data submission requirements in Section 12.1.

****Patients will be seen monthly for administration of zoledronic acid and for evaluation of adverse events (zoledronic acid is administered for an indefinite period of time and discontinued at the discretion of the treating physician). In year 2, patients will be seen a minimum of every 6 months. See Section 12.1 for data submission requirements.**

APPENDIX III

ZUBROD PERFORMANCE SCALE

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

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

APPENDIX IV (3/8/07)

RTOG 0517, Zometa® Shipment

Zometa® will be shipped by I.V. Solutions, Inc. only to institutions that have identified a single individual as responsible for receipt and accountability of shipments.

Sites must review Section 5.0 of the protocol to assure that all pre-registration requirements have been met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol)

U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Approved international institutions** must submit the SASF and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

The SASF must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) to process the form before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment. See Section 7.0 under "Drug Ordering and Accountability" for details regarding anticipated shipment and delivery timeframes.

APPENDIX V

CTSU LOGISTICS (11/7/08)

ADDRESS AND CONTACT INFORMATION FOR RTOG-0517

To submit site registration documents:	For patient enrollments:	Submit study data directly to the RTOG unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
<u>For patient eligibility questions:</u> Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3223. <u>For treatment-related questions:</u> Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.		
<u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org		
The CTSU Registered Member Web site is located at: http://members.ctsu.org		

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at <http://members.ctsu.org>.

All forms and documents associated with this study can be downloaded from the RTOG-0517 Web page on the CTSU registered member Web site (<http://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for RTOG-0517 site registration:

- For the initial shipment of zoledronic acid: Prior to registration of the institution's first case, institutions must fax the Study Agent Shipment Form (SASF) to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

Note: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Submit completed forms to the CTSU Regulatory Office:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Fax – 215-569-0206

Pre-study requirements for patient enrollment on RTOG-0517

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
 - CTSU Patient Enrollment Transmittal Form
 - RTOG-0517 Eligibility Checklist
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG within the confines of RTOG's registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0517 web page located on the CTSU registered member Web site (<http://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU.
3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG.
4. Please affix the RTOG study/case label to all source documentation and redact the patient's name.

SPECIAL MATERIALS OR SUBSTUDIES

Radiopharmaceuticals Modality Review (section 6.8)

- A quality assurance review to evaluate protocol compliance will be performed for all patients who receive or are to receive radiopharmaceuticals in this trial.

QOL– optional (section 11.4)

- Quality of Life assessment forms will be submitted as outlined in the protocol

SERIOUS ADVERSE EVENT (SAE) REPORTING

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (<http://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-0517 web page.
3. Do not send adverse event reports to the CTSU.

DRUG PROCUREMENT

Commercial Agents: *zoledronic acid; strontium-89; samarium-153; vitamin D; calcium supplement

*Zoledronic acid will be distributed by I.V. Solutions, Inc free of charge for this trial. Prior to registration of the institution's first case, institutions must fax the Study Agent Shipment Form (SASF) to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

1. Information on drug formulation, procurement, preparation, storage and accountability, administration, and potential toxicities are outlined in section 7.0 of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the RTOG 0517 Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.