RADIATION THERAPY ONCOLOGY GROUP

RTOG 0518

A PHASE III RANDOMIZED TRIAL TO EVALUATE THE EFFICACY OF ZOMETA® FOR THE PREVENTION OF OSTEOPOROSIS AND ASSOCIATED FRACTURES IN PATIENTS RECEIVING RADIATION THERAPY AND LONG TERM LHRH AGONISTS FOR HIGH-GRADE AND/OR LOCALLY ADVANCED PROSTATE CANCER

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0518

A Phase III Randomized Trial to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer

****SCHEMA (6/17/08)**

			For patients receiving concurrent
S	**DXA Scan T Score of Hip**	***R**	**radiation therapy and LHRH therapy**
T	1. < -1.0 but > -2.5	**A**	
R	2. ≥ -1.0	**N**	**Arm 1:**
A		**D**	Zoledronic acid q 6 months plus
T	**Duration of LHRH Therapy**	**O**	Vitamin D and calcium supplement
I	1. ≥ 1 year and ≤ 2.5 years	**M**	
F	2. > 2.5 years	**I**	**Arm 2:**
Y		**Z**	Vitamin D and calcium supplement
		E	

*See Section 5.1 for pre-registration requirements.

NOTE: It is mandatory that the treating physician determine the planned duration of LHRH therapy prior to the site registering the patient (minimum 1 year of therapy).

**See Sections 6.0 and 7.0 for details of treatment.

Patient Population: (See Section 3.0 for Eligibility) **[11/17/06]**

Histologically confirmed adenocarcinoma of the prostate; any one of the following clinical stages:

- ≥ T3 disease, any N stage, M0 with any Gleason score and any PSA;
- < T3 stage, any N stage, M0 with Gleason's score ≥ 8 and any PSA;
- < T3 stage, any N stage, M0 with Gleason's score 7 and PSA ≥ 15 nanograms/ml;
- < T3 stage, any N stage, M0 with Gleason score < 7 and PSA ≥ 20 nanograms/ml.

Required Sample Size: 1272

RTOG Institution # _____

RTOG 0518 **ELIGIBILITY CHECKLIST (3/22/07) (8/16/07) (3/13/08)**

Case # _____ (page 1 of 3)

_____(Y/N) 1. Did the patient start RT to the pelvis for prostate cancer?

_____ If yes, provide the date RT started

_____(Y) 2. Does the patient have a histologically or cytologically proven diagnosis of adenocarcinoma of the prostate within 12 months of registration?

_____(Y) 3. Does the patient have any one of the following clinical stages?
- ≥ T3 disease, any N stage, M0 with any Gleason score and any PSA;
- < T3 stage, any N stage, M0 with Gleason's score ≥ 8 and any PSA;
- < T3 stage, any N stage, M0 with Gleason's score 7 and PSA ≥ 15 nanograms/ml;
- < T3 stage, any N stage, M0 with Gleason score < 7 and PSA ≥ 20 nanograms/ml.

_____(Y) 4. Does the patient have a negative bone scan for metastatic disease?

_____(YN) 5. Has the planned duration of LHRH therapy begun?

_____(Y) If yes, did LHRH therapy begin ≤ 6 months prior to registration?

_____(Y) 6. Did the patient have a thorough physical assessment within 16 weeks prior to registration?

_____(Y) 7. Did the patient have a dental evaluation, including history of dental surgery within 16 weeks prior to registration?

_____(Y) 8. Was a bone scan done within 16 weeks of registration?

_____(Y) 9. Were T and L spine films done within 16 weeks of registration?

_____(Y) 10. Was a DXA scan done within 16 weeks of registration on Lunar, Hologic, or Norland equipment with T scores in both the L spine and total hip > negative 2.5?

_____(Y) 11. Is the Zubrod Performance Status 0-1 within 16 weeks prior to registration? (8/16/07)

_____(Y) 12. Is the patient ≥ 18 years of age?

_____(Y) 13. Are the lab parameters for corrected serum calcium and calculated creatinine clearance within the ranges and within the defined time frames specified in Section 3.1 and 3.2?

_____(Y) 14. Are patients who are sexually active willing/able to use medically acceptable forms of contraception?

_____(Y) 15. Has the patient agreed to refrain from using all products listed in Section 9.2, "Non-permitted Supportive Therapy"?

_____(Y) 16. Was the informed consent signed?

(Continued on the next page)

_____(Y/N) 17. Does patient have history of prior invasive malignancy other than prostate cancer, except non-melanomatous skin cancer?

_____(Y) If yes, has the patient been disease free for a period of three years?

_____(N) 18. Has the patient had prior bisphosphonate therapy?

_____(N) 19. Has the patient had prior pelvic radiation (other than for current prostate cancer) or prior radiotherapeutic agents, such as strontium or samarium?

_____(N) 20. Is the patient currently receiving systemic chemotherapy, steroids, growth hormones, or calcitonin?

_____(N) 21. Does the patient have a history of Paget's disease, uncontrolled thyroid or parathyroid dysfunction, or other diseases that influence bone metabolism?

_____(N) 22. Does the patient have a known hypersensitivity to zoledronic acid or other bisphosphonates?

_____(N) 23. Does the patient have active dental problems, including infection of the jaw, exposed bone or fixture trauma, or a current or prior diagnosis of osteonecrosis of the jaw, exposed bone in the mouth, or slow healing after dental procedures?

_____(N) 24. Has there been recent (within 6 weeks of study entry) dental or jaw surgery (e.g., extraction, implants) or is this surgery planned?

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

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

(Continued on the next page)

RTOG Institution # _____

RTOG 0518 **ELIGIBILITY CHECKLIST (3/22/07) (3/13/08)**

Case # _____ (page 3 of 3)

_____ 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 (scheduled date of first zoledronic acid)

_____ 17. Randomization Date (This date will be populated automatically.)

_____ 18. Medical Oncologist's Name

_____ 19. Specify DXA scan T score of hip (< -1.0 but > -2.5 vs. ≥ - 1.0)

_____ 20. Specify duration of LHRH therapy (≥ 1 year and ≤ 2.5 years vs. > 2.5 years)

_____(N/Y) 21. Did the patient agree to participate in the Quality of Life component of the study?

_____(NA/N/Y) 22. Is the patient's health care covered at least in part by Medicare (and therefore, will Medicare data be used for health utility research in this study)?

If yes, provide the patient's social security number:_____

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

1.1 Background

The RTOG studies 85-31, 86-10, and 92-02, as well as other data have shown that the use of androgen deprivation therapy (ADT) in conjunction with radiation therapy for locally advanced and/or high-grade adenocarcinoma of the prostate increases disease-free survival and in the case of 85-31, overall and disease-specific survival.[1-4] But studies evaluating patients who have utilized LHRH agonists have shown an increase in the incidence of osteoporosis.[5-7] This increase in incidence of osteoporosis has translated into an increase in fracture risk.[8-11] The risk of osteoporosis associated fractures (defined in this study as any fractures of the bone) increases as the length of hormonal manipulation increases.[9] These fractures not only affect patient's quality of life, but in the case of hip fractures, are associated with increased mortality.[12] Decreasing the fracture rate, therefore, would be important in this population of prostate cancer patients.

Both testosterone and estrogen are responsible for regulating bone metabolism, although estrogen appears to play a more dominant role.[12] In men, estrogen levels are dependent on testosterone levels as estrogen is a result of the metabolism of testosterone. LHRH agonists cause testosterone levels to fall by more than 95%, resulting in decreased estradiol levels. These hormonal changes result in an increase of osteoclastic activity[13] and subsequently, osteoporosis and associated fractures.

1.2 Bisphosphonates

Bisphosphonates are effective inhibitors of osteoclastic bone resorption and have demonstrated therapeutic efficacy in the treatments of hypercalcemia of malignancy, lytic bone disease associated with multiple myeloma, and mixed lytic bone metastasis associated with breast cancer.[14-38] Osteoclasts are special bone cells which erode mineralized bone by secreting acids and liposome enzymes. In normal bone remodeling, osteoclastic bone resorption is coupled to and is in equilibrium with osteoblastic bone formation.[39] In osteoporosis, the balance of osteoclastic and osteoblastic activity is interrupted such that bone resorption occurs.

Bisphosphonates have shown efficacy in osteoporosis because their mechanism of action inhibits osteoclastic function. The precise mechanism by which bisphosphonates inhibit osteoclast function is not fully understood, but may include a direct toxic affect on mature osteoclasts, an inhibition of osteoclasts production from precursor cells, and an impairment of osteoclasts chemotaxis to sites of active bone resorption.[40-49] Their ability to prevent osteoporosis and associated fractures in breast cancer and multiple myeloma has been well studied. Yet there is a paucity of such data in prostate cancer patients.[5, 50] Because of the lack of data, the current standard of care for prostate cancer patients receiving long term LHRH therapy does not include bisphosphonate therapy.

Prostate cancer patients with locally advanced non-metastatic disease who received radiation and long term LHRH therapy (i.e., > 1 year) are a unique population in that they are at risk of osteoporosis of their pelvic bones from androgen deprivation therapy as well as experiencing the effects of radiation. Therefore, these patients are at the highest risk for development of osteoporosis associated fractures and provide a most appropriate population to study the potential benefits of intravenous bisphosphonates in a large prospective randomized trial.

More recent data confirms the fact that osteoporosis is an important clinical entity in patients with prostate cancer receiving androgen deprivation therapy and that this therapy causes osteoporotic fractures. These data also confirm the need to assess patients for osteoporosis and recommend intervention.[51-53] Calcium and vitamin D supplementation have been shown to increase bone density and are recommended for this patient population.[53] Whether bisphosphonate therapy is needed beyond vitamin D and calcium is still not known but many authors encourage its evaluation as is done in this clinical trial.[51-52]

1.3 Zometa® (Zoledronic Acid)

Bisphosphonates differ from one another by substitution of active side chains on their phosphorous - carbon - phosphorous structural backbone.[54] 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.[54-55] Zometa®, a 3rd generation bisphosphonate, is 2-(imidazol-l-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.[56-57] 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].[58] 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.[56]

Phase I clinical trials also have provided evidence of the potency of Zometa® to inhibit osteoclastic bone resorption.[59-60] 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 that 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.[34] Also, an ongoing phase II study indicates that long term therapy with Zometa® administered in short 15 minute infusions is well tolerated.[57]

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.[61] Even when lower doses of these agents are infused slowly, they can still cause transient changes in renal function.[62] 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.[17, 63-64] 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.[56]

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.

Thus, Zometa® is an appropriate bisphosphonate to study the potential benefit of bisphosphonates in preventing osteoporotic fractures associated with LHRH therapy.

1.4 Phase III Clinical Trial with Zometa® in Patients with Metastatic Prostate Cancer

Three large phase III trials performed with Zometa® (4 mg or 8 mg) support its efficacy and safety in patients with bone metastases due to a range of tumor types.[65-67] One of these trials specifically evaluated Zometa®, 4 mg or 8 mg, vs. placebo in men with hormone-refractory prostate cancer metastatic to bone.[67] Patients received either Zometa® 4mg (N=214), 8 mg

(N=221), or placebo (N=208) for up to 15 months. Standard antineoplastic therapy was allowed. The primary endpoint was the proportion of patients having at least one skeletal-related event (SRE). SREs were defined as pathologic bone fractures, radiation therapy to bone (including the use of radioisotopes), spinal cord compression, surgery to bone, or a change of antineoplastic therapy to treat bone pain. Time to first SRE, skeletal morbidity rate (SMR) and time to multiple occurrences of SREs were the other major skeletal endpoints. Following a protocol amendment, the infusion time for Zometa® was increased from 5 to 15 minutes, and infusate volume increased from 50 to 100 mL during the trial. In another protocol amendment, all patients on 8 mg Zometa® were switched to 4 mg (subsequently termed the 8/4 mg group), and creatinine monitoring was instituted. Both amendments were instituted to increase renal safety.

The effect of Zometa® was similar in the 4 mg and 8/4 mg treatment groups. The Zometa® 4 mg group showed a 25% relative reduction in SREs at 15 months (33% versus 44%; p = 0.021). The incidence of SREs in the 8/4 mg group, although lower than in the placebo group, was not statistically different (38% vs 44%, p=0.222). Even when asymptomatic fractures (such as radiologically assessed vertebral fractures) were not counted as a SRE, the overall incidence of SREs remained lower in the Zometa® 4 mg (28%) and Zometa® 8/4 mg (31%) treatment groups than in the placebo group (38%).

Zometa® 4 mg also significantly delayed time to first SRE (p = 0.011), time to first pathological fracture (p = 0.011), reduced the proportion of patients with a pathological fracture (p = 0.009), decreased the SMR, and produced a sustained suppression of markers of bone resorption and formation.

Since the time to first SRE analysis did not take into account subsequent SREs, time to multiple occurrences of SREs was analyzed using the Anderson-Gill approach. There was a statistically significant difference between the Zometa® 4 mg group and the placebo group in the time to multiple occurrence of SREs in favor of the Zometa® 4 mg group (p=0.004).

Fatigue, anemia, myalgia, fever, lower limb edema, and possibly anorexia and weight decrease occurred more often with Zometa® than placebo. Grade 3 or 4 hypocalcemia occurred in approximately 2% of patients treated with Zometa®. Grade 3 or 4 decreases in hemoglobin concentration occurred in 4.6% of patients in the Zometa® 4 mg and placebo groups and in 9.7% of patients in the Zometa® 8/4 mg group.

Renal adverse events were reviewed separately due to the concern about renal toxicity. Using a fifteen-minute infusion, the proportion of patients with renal adverse events (AEs) was approximately 31% in the Zometa® 4 mg and placebo groups, and 38% in the 8/4 mg group. Acute renal failure and renal impairment were still reported in a slightly higher number of Zometa® 4 mg patients than placebo patients (5.2% vs 0% and 7.2% vs 3.6%, respectively). However, acute renal failure was suspected to be study drug-related in only 0.5% of patients in both the Zometa® 4 mg and placebo groups. Renal impairment was suspected to be study drug-related in 2.8% and 0% patients in the Zometa® 4 mg and placebo groups, respectively. With a fifteen-minute infusion, renal function deterioration (defined as a specified increase from baseline in serum creatinine) occurred in 15.2%, 20.7%, and 11.5% of patients in the Zometa® 4 mg and 8/4 mg groups, and the placebo group, respectively. Based on Kaplan-Meier estimates of time to first renal function deterioration, the risk ratio was 1.066 (95% CI 0.745, 1.526, p=0.882) for the Zometa® 4 mg group vs. the placebo group, indicating comparable risk.

1.5 Clinical Studies in Prevention of Bone Loss in Prostate Cancer

Smith et al performed a prospective, randomized, open-label trial comparing pamidronate to no treatment in 47 men with locally advanced, lymph-node positive or recurrent prostate cancer.[50] Patients in this study did not have bone metastases at baseline. All men in this study received leuprolide, with or without addition of 60 mg infusions of pamidronate given every 12 weeks for 48 weeks. Mean bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) increased less than 1% with pamidronate at all measured sites. The differences between the pamidronate and placebo groups in BMD at the lumbar spine (p < 0.001), trochanter (p < 0.003), and total hip (p = 0.005), were statistically significant, however. Femoral neck BMD increased less than 1% in either group. Mean trabecular lumbar spine BMD measured by quantitative computerized tomography decreased from baseline by only 2.0% in men receiving pamidronate, but by 8.5% in men receiving leuprolide alone (p < 0.001).

In a subsequent randomized, double-blind, placebo-controlled trial of Zometa® in men with nonmetastatic prostate cancer who were just beginning ADT, Smith, et al observed significant increases in BMD of the spine and hip after one year.[68] This is in contrast to the results with pamidronate, which showed stabilization but not an increase in BMD in a similar patient population. In the Zometa® study, 106 men treated with a LHRH agonist with or without an antiandrogen were randomized to receive 4 mg Zometa® intravenously or a placebo infusion every 3 months for one year. The median age of the population was 72-73 years and the average time since initial diagnosis was approximately 30 months. Lumbar spine BMD increased by 5.6% in men receiving Zometa® compared with a decrease of 2.2% in men receiving placebo ($p < 0.001$). Results with Zometa® and placebo showed the same pattern for the patients with normal BMD at baseline (N = 46) and those with osteopenia (BMD between –1 and –3.0 standard deviations from peak young normal BMD values, N = 21). Men with a BMD that fell more than 3.0 standard deviations below normal were excluded from the study. Total hip BMD, trochanteric BMD, and femoral neck BMD each decreased by more than 2% in the placebo group and increased by 1.1%, 2.2% and 1.2%, respectively in the Zometa® group ($p < 0.001$, $p = 0.001$, and $p = 0.011$, respectively, for between group comparisons).

Treatment was well tolerated, with no evidence of renal toxicity. The most commonly reported adverse events in the Zometa® group were hot flushes (58%), fatigue (38%), arthralgia (22%), and constipation (16%), while these adverse events occurred in 51%, 35%, 14%, and 16%, respectively, of patients in the placebo group. Severe (grade 3 or 4) adverse events were reported in 24% of men in the Zometa® group and 39% of men in the placebo group. Limb pain and weakness were each reported in 13% of men in the Zometa® group compared with 8% and 0%, respectively, of men in the placebo group.

Zometa® had no effect on PSA or testosterone levels, which were similar between the two treatment groups during and at the end of treatment.

In summary, this trial demonstrated for the first time the ability of Zometa® to significantly increase BMD in men with nonmetastatic prostate cancer when started concurrently with initiation of ADT.

1.6 Quality of Life

Osteoporosis is a major cause of disability and pain in older adults, with a negative effect on ability to perform household and self-care activities. Prostate cancer patients who received radiation and long-term LHRH therapy are a unique population, in that their pelvic bones see the effects of osteoporosis from androgen deprivation therapy as well as the effects of radiation. Thus, they are at increased risk of developing osteoporosis, with resultant fractures, disability, and pain. Examination of the health-related quality of life (QOL) will provide additional rationale for the use of bisphosphonate therapy in this population. Furthermore, evaluation of the quality of life in a population of men with treatment-induced osteoporosis will add an important element missing in the current literature.

The QOL component of this study will include two measures, the Functional Assessment of Cancer Therapy-General (FACT-G) and the EuroQol (EQ-5D). These assessments will be administered pre-treatment and every 6 months during treatment for 3 years.

1.6.1 *General Quality of Life*

Quality of life will be measured using the Functional Assessment of Cancer Therapy-General (FACT-G, version 4.0)[69] The FACT-G, used as a QOL measure in the majority of RTOG studies, 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). There are extensive data regarding the psychometric strengths of this measure. The FACT-G takes between 5 and 10 minutes to complete and has been written at the 4th grade level.[70] The FACT-G is scored by summing the individual scale scores, with higher scores indicating better quality of life.

1.6.2 *Multi-Attribute Health Utility Measurement Using the EuroQol (EQ-5D)*

Although developed in Europe, the EQ-5D has been used in the United States and Canada.[71-74] The EQ-5D is a method for obtaining valuations of HRQOL. It also can be used as an adjustment to survival and in cost-utility analysis. It is a two-part questionnaire that the patient can complete in approximately 5 minutes.[75] The first part of the EQ-5D consists of five items

covering five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on three levels: 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 (3 to the 5th) health states to which unconsciousness and death are added.[76] The second part is a visual analogue scale (VAS) valuing current health state, measured on a ten-point interval scale (the scale measures approximately 20 cm). 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.[77] Quality adjusted survival is the weighted sum of different time in different health states added up to a total quality-adjusted survival time [U= sum of quality (qi) of K health states times the duration (si) spent in each health state.][78]

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate the potential benefit of bisphosphonate therapy in the prevention of bone fracture (defined as any fractures of the bone) in patients receiving LHRH and radiation therapy for locally advanced adenocarcinoma of the prostate

2.2 Secondary Objectives (3/13/08)

2.2.1 To evaluate the potential benefit in quality of life for patients receiving bisphosphonate therapy in addition to LHRH and radiation therapy for locally advanced non-metastatic adenocarcinoma of the prostate;

2.2.2 To evaluate the potential benefit in bone mineral density (BMD) over a period of three years for patients receiving bisphosphonate therapy in addition to LHRH and radiation therapy for locally advanced non-metastatic adenocarcinoma of the prostate.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (3/22/07) (8/16/07) (3/13/08)

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of adenocarcinoma of the prostate within 12 months of registration;

3.1.2 Any one of the following clinical stages:

- ≥ T3 disease, any N stage, M0 with any Gleason score and any PSA;
- < T3 stage, any N stage, M0 with Gleason's score ≥ 8 and any PSA;
- < T3 stage, any N stage, M0 with Gleason's score 7 and PSA ≥ 15 nanograms/ml;
- < T3 stage, any N stage, M0 with Gleason score < 7 and PSA ≥ 20 nanograms/ml.

3.1.3 A negative bone scan for metastatic disease;

3.1.4 It is mandatory that the treating physician determine the planned duration of LHRH therapy prior to the site registering the patient (minimum 1 year of therapy);

3.1.5 If patient is receiving pre-treatment LHRH therapy, it must have begun ≤ 6 months prior to registration. If pelvic RT has started, it must have begun ≤ 8 weeks prior to registration;

3.1.6 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup to be done <u>within 16 weeks prior to registration</u>:

3.1.6.1 History/physical examination;

3.1.6.2 Dental evaluation, including history of dental surgery (e.g., extraction or implant);

3.1.6.3 Bone scan;

3.1.6.4 T and L spine films;

3.1.6.5 DXA scan: To be eligible the patient must have a scan on Lunar, Hologic, or Norland equipment only and the T scores in both the L spine and total hip must be > negative 2.5;

3.1.7 Zubrod Performance Status 0-1 within 16 weeks prior to registration; (8/16/07)

3.1.8 Age ≥ 18;

3.1.9 Serum creatinine within 4 weeks prior to registration (8/16/07)

3.1.10 Corrected serum calcium ≥ 8.4 and ≤ 10.6 mg/dl within 8 weeks prior to registration; **note**: for patients with an albumin of 4.0, corrected calcium=measured calcium. The formula for corrected calcium if serum albumin value is above or below 4.0 is as follows:

Corrected calcium (mg/dl) = (4 – [patient's albumin (g/dl)] x 0.8) + patient's measured calcium (mg/dl)

3.1.11 Patients who are sexually active must be willing/able to use medically acceptable forms of contraception, as the treatment involved in this study may be significantly teratogenic.

3.1.12 Patient agrees to refrain from using all products listed in Section 9.2, "Non-permitted Supportive Therapy";

3.1.13 Post-prostatectomy patients are eligible.

3.1.14 Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (3/22/07)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; e.g., carcinoma in situ of the breast or oral cavity are permissible;

3.2.2 Patients with baseline T scores of ≤ -2.5 are excluded.

3.2.3 Patients with baseline calculated creatinine clearance < 30 mL/min (estimated by Cockcroft-Gault formula below) are excluded.

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

3.2.4 Prior bisphosphonate therapy;

3.2.5 Prior pelvic radiation (other than for current prostate cancer) or prior systemic radiotherapeutic agents, such as strontium or samarium;

3.2.6 Patients receiving systemic chemotherapy, steroids, growth hormones, or calcitonin;

3.2.7 Patients with a history of Paget's disease or with uncontrolled thyroid or parathyroid dysfunction or with other diseases that influence bone metabolism;

3.2.8 Known hypersensitivity to zoledronic acid or other bisphosphonates;

3.2.9 Active dental problems at study entry, including infection of the teeth or jawbone; dental or fixture trauma; or a current or prior diagnosis of osteonecrosis of the jaw, exposed bone in the mouth, or slow healing after dental procedures;

3.2.10 Recent or planned (within 6 weeks of study entry) dental or jaw surgery (e.g., extraction, implants).

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT (11/17/06)

(In addition to the mandatory pre-testing for eligibility in Section 3.0)

Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient's eligibility for this study, document on the appropriate case report form.

4.1 Additional Mandatory Pre-treatment Evaluations/Interventions

See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation:

4.1.1 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) and the EuroQol (EQ-5D).

4.1.2 The patient's medical history will include current use of statins. Sites will document name of drug and daily dose.

4.2 Additional Highly Recommended Pre-treatment Evaluations/Interventions

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial, but not mandatory:

4.2.2 Assessment of weight and general nutritional status

5.0 REGISTRATION PROCEDURES (3/13/08)

NOTE: It is mandatory that the treating physician determine the planned duration of LHRH therapy prior to the site registering the patient.

5.1 *Regulatory Pre-Registration Requirements*

5.1.1 **U.S. sites and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.1.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

5.1.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.1.2.2 Note: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See **http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc**

Approved international sites fax copies of the documentation below, along with the completed International REC Certification Form (**http://www.rtog.org/pdf_forms.html?members/forms=RTOG%20International%20REC%20Certification.doc**) to RTOG Headquarters (215-574-0300) prior to registration of the institution's first case:

- REC approval letter;
- Informed Consent (English Version);
- Federalwide Assurance (FWA) number.

5.1.3 *Pre-Registration Requirements for the Initial Shipment of Zometa:*

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. After receipt of written approval of submitted LOI forms from RTOG Headquarters, 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.

Institutions 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 must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- 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: e-mail 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 RADIATION THERAPY

Radiation therapy must be planned for the patient. Patients may receive external beam irradiation, brachytherapy (HDR or LDR), or a combination of external beam irradiation and brachytherapy at the discretion of the treating physician. Dose/duration also will be at the discretion of the treating physician; however, dose will not exceed 45 Gy to 100% of the proximal femur, and no proximal femur will receive ≥ 60 Gy. Patients on this study are eligible for other RTOG trials involving radiation therapy alone.

6.1 Documentation Requirements

Dose volume histograms (DVHs) will be submitted to RTOG Headquarters for the following:

- Right proximal femur, defined as the top of the lesser trochanter through the entire of the femoral head;
- Left proximal femur, as defined by the top of the lesser trochanter through the entire of the femoral head;
- Bladder;
- Rectum, defined from just caudad to the sigmoid colon to the bottom of the obturator foramen.

6.2 Radiation Adverse Events

Adverse events include: skin reactions; hair loss in treatment area; transitory tiredness; infertility; impotence that could be permanent; urethral scar tissue; small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, rectal bleeding, hematochezia, and bowel incontinence; bladder complications including urinary frequency, urgency, dysuria, hematuria, urinary tract infections, and urinary incontinence; injuries to the rectum, bowel, or urinary system that could result in colostomy or other major surgical procedures.

6.3 Radiation Adverse Event Reporting

See Section 7.9 for Adverse Event Reporting.

7.0 DRUG THERAPY (3/22/07) (3/13/08)

Patients should not be receiving concurrent systemic chemotherapy; see Section 3.2.6.

7.1 LHRH Therapy

LHRH therapy must be planned for the patient, and LHRH therapy must take place for a minimum of one year. Choice of LHRH agonist (e.g., leuprolide, goserelin, buserelin, or triptorelin), dose, and duration are at the discretion of the treating physician. **NOTE**: It is mandatory that the treating physician determine the planned duration of LHRH therapy (≥ 1 year and ≤ 2.5 years vs. > 2.5 years) prior to the site registering the patient, as duration is a stratification variable for this study (see Section 5.0).

7.1.1 *Description*: LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone. Analogs approved by the FDA (or by Health Canada for Canadian institutions) can be used in this study.

7.1.2 *Supply*: Commercially available. (NOTE: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries outside of the United States.)

7.1.3 *Storage*: LHRH analogs should be stored as directed by the commercial supplier.

7.1.4 *Administration*: LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eligard), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer's instructions should be followed.

7.1.5 *Adverse Events*: Consult the package insert for comprehensive adverse event information. Class-related adverse events are generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances have

occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms. Other side effects include impotence and loss of libido, weight gain, depression, dizziness, loss of bone density, anemia, increased thirst and urination, unusual taste in the mouth, skin redness or hives, pain at injection site, and muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, nausea, vomiting, and rarely allergic generalized rash and difficulty breathing.

7.2 Protocol Treatment: Zoledronic Acid (6/17/08)

Note: All cases registered prior to Amendment 4 (Version Date: March 13, 2008; Broadcast Date: April 24, 2008) were unblinded (see Section 7.7) and re-assigned to the modified treatment arms. Patients who were on the placebo Arm prior to Amendment 4 will be in the observation Arm (Arm 2) and will take Vitamin D and calcium supplements only. Patients on the zoledronic acid Arm prior to Amendment 4 will remain on the zoledronic acid Arm (Arm 1) and will take zoledronic acid every 6 months plus Vitamin D and calcium supplements.

7.2.1 *Arm 1: Zoledronic Acid* (3/22/07)

Within 1 month of registration, patients on Arm 1 will receive the first dose of zoledronic acid intravenously. Due to scheduling, this first dose can occur immediately prior to starting concurrent radiation therapy and LHRH therapy or any time during this one month period.

All patients in Arm 1 will receive zoledronic acid every 6 months, for a total of 3 years or 6 infusions.

Patients also will take 400 IU of vitamin D and 500 mg of calcium orally, daily for 3 years, starting within 1 month of registration. 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.

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 creatinine clearance at baseline. The starting dose for each patient will be continued throughout the study. Subsequent doses may be held based on serum creatinine measurements on study, but there will be no dose modifications after a patient's starting dose is established. See Section 7.6 for details.

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

7.3.1 *Formulation*

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

7.3.2 *Preparation* (1/11/07)

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.

7.3.3 *Administration* (11/17/06)

Patients must be evaluated prior to and following the administration of the Zometa® infusion to ensure that they are adequately hydrated. Serum creatinine will be measured within 7 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 creatinine clearance at baseline. The starting dose for each patient will be continued throughout the study. Subsequent doses may be held based on serum creatinine measurements on study, but there will be no dose modifications after a patient's starting dose is established. 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.

7.3.4 *Adverse Events*

Consult the package insert for comprehensive adverse event information. Based on information from subjects given Zometa® in clinical trials, the potential adverse events 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, leukopenia
- 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 jaws. 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.

7.3.5 *Storage and Stability* **(3/22/07)**

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 2-8ºC. 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.

7.3.6 *Supply* **(1/11/07)**

Zometa® will be manufactured and packaged by Novartis and provided to patients on study free of charge.

7.3.7 *Drug Ordering and Accountability* **(1/11/07) (6/17/08) (6/26/08)**

Zometa® with label and tubing and 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 six shipments (two shipments each year). **U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) and fax the form 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. 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.

NOTE: The SASF for this study is available on the RTOG web site, http://www.rtog.org, next to the protocol.

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.

7.4 Vitamin D

7.4.1 *Formulation*

Vitamin D analogs are fat-soluble vitamins.

7.4.2 *Administration* **(11/17/06)**

The patient will take vitamin D, 400 IU (10µg), orally each day for 3 years.

7.4.3 *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

7.4.4 *Contraindications*

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

7.4.5 *Storage*

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

7.4.6 *Supply*

Commercially available

7.5 Calcium

7.5.1 *Formulation*

Calcium is available in a wide range of preparations.

7.5.2 *Administration* **(11/17/06)**

A single dose of 500 mg of elemental calcium is administered orally each day for 3 years.

7.5.3 *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

7.5.4 *Contraindications*

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

7.5.5 *Drug Interactions*

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

7.5.6 *Storage*

Calcium should be stored as directed by the commercial supplier.

7.5.7 *Supply*

Commercially available

7.6 Dose Modifications: Zoledronic Acid (3/22/07)

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 creatinine clearance at baseline (see parameters below) estimated by Cockcroft-Gault formula. The starting dose for each patient will be continued throughout the study. Subsequent doses may be held based on serum creatinine measurements on study, but there will be no dose modifications after a patient's starting dose is established.

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

Note: The patient's actual weight, rather than "ideal" weight, should be used to calculate creatinine clearance. 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 mg/min	3 mg

Note: The starting dose for each patient will be continued throughout the study. Subsequent doses may be held based on serum creatinine measurements on study, but there will be no dose modifications after a patient's starting dose is established.

7.6.1 *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 baseline 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 baseline value. For patients who require a delay, the delay will be a 6 month delay such that if a patient has serum creatinine changes that require a delay, the dose will be skipped for that particular 6 month period of time and assessment will occur again at the regular scheduled subsequent 6 month visit. Serum creatinine will be checked within a week of that next dosing time and parameters listed above will be followed.

7.6.2 *Delay or Discontinuation of Other Therapies*

If radiation therapy is delayed, or patients stop LHRH therapy, or patients fail to take vitamin D or calcium supplements, they will continue to receive zoledronic acid per protocol.

7.7 Code Breaks (6/17/08)

The blinded treatment assignments for patients registered to the study prior to Amendment 4 (Version Date: March 13, 2008; Broadcast Date: April 24, 2008) were unblinded by the study statistician. Sites were notified by email of cases that should be moved from the placebo Arm to the observation Arm (Arm 2) or from the every 3 month Zometa schedule to the every 6 month Zometa schedule (Arm 1). In the email, sites were asked to confirm their compliance.

7.8 Complementary Therapy Reviews

The Principal Investigator, Colleen Lawton, M.D. and the Medical Oncology Co-Chair, Matthew Smith, M.D., 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.

Drs. Lawton and Smith will perform a Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. Drs. Lawton and Smith 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.

7.9 Adverse Events (9/7/11)

Beginning October 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4 for AdEERS reporting of adverse events (AEs). **All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF.** The CTCAE version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

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

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) 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.

7.9.1 Adverse Events (AEs) (11/17/06)

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*. December 2004.]

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 via AdEERS. Use the patient's case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also **must be reported on the AE case report form** (see Section 12.1). **NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.**

7.9.2 **(11/17/06) <u>Serious Adverse Events (SAEs)</u> — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS within 24 hours of discovery of the event.**

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;
  2. Osteomyelitis (of any bone).

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 drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [*CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements*. December 2004.]

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to 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. **All forms** (and supporting source documentation) **submitted to RTOG Headquarters must include the RTOG study/ case numbers**; non-RTOG intergroup study and case numbers must 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 print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.9.3 **<u>Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)</u> (9/7/11)**

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

7.10 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 Days[1] of the Last Dose of the Investigational Agent, Zometa®, in this Study

	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

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a 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.

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

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

9.2 Non-permitted Supportive Therapy

9.2.1 Patients on this study should not be receiving steroids, growth hormones, or calcitonin.

10.0 TISSUE/SPECIMEN SUBMISSION

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (11/17/06) (8/16/07) (3/13/08) (6/17/08)

Assessments	Pre-Study Entry	6 Months After First Dose of Zoledronic Acid or 6 Months Post-Study Entry	At 6 Months	At 18 Months	Follow Up[i]
History[k]/physical	X[a]	X[k]	X[k]	X[k]	X[k]
Weight	X[a]	X	X		X
Zubrod	X[a]	X	X		X
Dental Evaluation[d]	X[a]				X[j]
Bone scan	X[a]				
T and L spine films[e]	X[a]				X
DXA scan[f]	X[a]			X	X
Serum calcium[l], albumin[l]	X[b]	X	X		
Serum creatinine[l]	X[c]	X	X		
FACT-G[h]	X[g]	X	X	X	X
EQ-5D[h]	X[g]	X	X	X	X

a) Within 16 weeks of registration;
b) Within 8 weeks of registration
c) Within 4 weeks of registration;
d) Including history of dental surgery (e.g., extraction or implant) within 1 year prior to study entry;
e) **NOTE**: If the patient is removed from treatment due to fractures, T and L spine films should be done for comparison to baseline films;
f) Sites will submit the DXA Scan Report to RTOG Headquarters and the DXA Scan Data Form (see Section 12.1), which will include: Manufacturer (Lunar, Hologic, or Norland equipment only), Model, Age of software, BMD in g/cm^2 in L spine and hip, T score of L spine and hip;
g) 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.
h) If the patient consents to participate in the quality of life component of the study, QOL assessments (FACT-G, EQ-5D) will be administered every 6 months for 3 years; (8/16/07)
i) Follow up is done at 18 months as well as at 3 years;
j) Including history of dental surgery (e.g., extraction or implant) since last dose of zoledronic acid.
k) Medical history will include current use of statins. Sites will document name of drug and daily dose pre-study entry and at each follow-up visit.
l) After patients are registered on study, these labs will be conducted for Arm 1 (zoledronic acid) patients only.

11.2 Criteria for Removal from Protocol Treatment (11/17/06)

11.2.1 Any bone fracture (defined as any fractures of the bone); **NOTE**: The patient should have T and L spine films at this time. The patient may be unblinded (see Section 7.7 for criteria), and subsequent treatment is at the discretion of the treating physician.

11.2.2 Adverse events unacceptable 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;

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

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

11.3 Quality of Life Assessments

11.3.1 *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.

11.3.2 *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 (3/13/08)

Data should be submitted to:

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

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

12.1 Summary of Data Submission (11/17/06)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** FACT-G **(PQ)** Health Utility Measurement (EQ-5D) **[HP]**	Within 2 weeks of study entry
Dosimetry Information Dose Volume Histogram **(DV)** Radiotherapy Form **(T1)**	Within 1 week of RT end
DXA Scan Report **(DR)** DXA Scan Data Form **(DA)**	Within 16 weeks of registration, at 18 months, and at 3 years
Treatment Form **(TF)**	Every 6 months from start of treatment for 36 months
Follow-up Form **(F1)**	At 18 months and 36 months from start of treatment
FACT-G **(PQ)** Health Utility Measurement (EQ-5D) **[HP]**	Every 6 months from start of treatment for 3 years

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 *Primary Endpoint*

Freedom from any bone fracture (FABF): The time of failure will be measured from the date of randomization to the date of documented bone fracture(s), defined as any fractures of the bone.

13.1.2 *Secondary Endpoints*

13.1.2.1 Percent change in bone mineral density (BMD) at three years;

13.1.2.2 Changes in Quality of Life using FACT-G;

13.1.2.3 Evaluate the utility (as measured by the EQ5D) of the use of bisphosphonates.

13.2 Sample Size (3/13/08)

13.2.1 *Stratification and Randomization*

Patients will be stratified before randomization according to DXA Scan T Score of the Hip (< -1.0 but > -2.5 vs. ≥ - 1.0) and Duration of LHRH therapy (≥ 1 year and ≤ 2.5 years vs. > 2.5 years). The treatment allocation scheme described by Zelen[79] will be used because it balances patient factors other than institution. Patients receiving concurrent radiation therapy and LHRH therapy will be randomized to either Zometa® or observational control. Vitamin D and calcium supplements will be given to all patients.

13.2.2 *Sample Size Derivation* **(6/17/08)**

The sample size calculations will address the specific primary hypothesis that receiving Zometa® in addition to concurrent radiation and LHRH therapy with vitamin D and calcium supplements will improve the probability of remaining free of any bone fracture (FABF), defined as any fractures of the bone, at 3 years compared to similarly treated patients receiving only concurrent radiation and LHRH therapy with vitamin D and calcium supplements. This is the same as reducing the probability of any bone fracture (ABF) at 3 years (i.e., ABF = 1- FABF). The primary null hypothesis can be written as,

$$H_0: FABF_{Zometa®}(t) \leq FABF_{Control}(t)$$

where t is time and $FABF_{Control}$ and $FABF_{Zometa®}$ are the freedom from any bone fracture for the observational control and Zometa® arms, respectively

The clinical experience of Krupski, et al.[80] showed a probability of any fracture at 3 years in 25% of men with prostate cancer receiving androgen deprivation therapy. Because there is limited information on the failure rate of osteoporosis associated bone fractures in this population, we chose any fractures of the bone as the primary endpoint. We assume that the control arm will have a three-year FABF rate of 88% (or a three-year ABF failure rate of 12%) translating to a yearly ABF hazard rate of 0.0426. The study is designed to show a 40% relative reduction in the yearly ABF hazard rate, i.e., a three-year FABF rate of 92.6% (or a three-year ABF failure rate of 7.4%, yearly ABF hazard rate of 0.0256). This translates to a 4.6% absolute improvement in the probability of remaining free of any bone fracture at 3 years. The following assumptions and parameters were used to determine the required number of any bone fractures and patients for the primary endpoint:

- The probability of remaining free of ABF on the control arm is 88% (the probability of an ABF is 12%).
- A design effect of 40%, that is, a relative reduction in the yearly ABF hazard rate of at least 40% in the Zometa® arm, from 0.0426 to 0.0256.
- One-sided test at $\alpha = 0.05$.
- Statistical power of 80%.
- One interim analysis and a final analysis for efficacy using Haybittle-Peto boundaries.[81]

Using a log-rank test and the same number of patients in each treatment arm, 101 bone fractures (any fracture) are required with a total of 1030 patients. Guarding against an ineligible rate of 10% and a drop-out rate of 10% for interim DXA scans and clinician/patient preferences, **the final targeted accrual for this study will be 1272 cases.**

13.2.3 *Power Calculations for Secondary Endpoints*

13.2.3.1 Percent Change in Bone Mineral Density (BMD) at Three Years

The clinical experience from Smith et al.[68] showed a statistically significant difference of 7.8% in mean percent change from baseline in bone mineral density (BMD) at 1 year with zoledronic acid compared to placebo ($p < 0.001$). With 1030 eligible and analyzable patients, the statistical power to detect a clinically meaningful improvement in mean percent change from baseline in BMD using Zometa® is shown in Table 1, assuming that the standard deviations for the Zometa and control groups based on data from Smith, et al. are 4.733 and 5.248, respectively and using a two group Satterthwaite t-test with a 0.05 one-sided significance level. Thus, we would have at least 94% statistical power to detect a mean percent change improvement in BMD of 1 at 3 years.

Table 1: Statistical Power for a Mean Percent Change Improvement in BMD at 3 Years

Mean Difference	Statistical Power
0.1	9.3%
0.2	15.9%
0.3	25.1%
0.4	36.4%
0.5	49.0%
0.6	61.8%
0.7	73.3%
0.8	82.8%
0.9	89.8%
1.0	94.5%
1.1	97.3%
1.2	98.8%
1.3	99.5%
1.4	99.8%
1.5	>99.9%

13.2.3.2 *Quality of Life*

General Quality of Life (QOL) will be measured using the Functional Assessment of Cancer Therapy-General (FACT-G, version 4.0).[69] Health Related Quality of Life (HRQOL) and health utility will be measured using the EuroQoL (EQ-5D).[71-73] These tools will be administered pre-treatment and every 6 months during treatment for 3 years.

13.3 Patient Accrual

Based on patient accrual in previous RTOG randomized prostate 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 17.7 cases per month (or 212 cases per year), based on the accrual patterns of completed RTOG prostate cancer treatment protocols. We expect to complete the accrual in 6 years. The total duration of the study is expected to be 9 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 4 cases per month, the study will be re-evaluated for its feasibility. If the study is continued after 18 months with fewer than 4 cases per month and then at 24 months after study activation, if the average monthly accrual between 19 and 24 months is less than 4 patients per month, i.e., less than 20% of the projected 17.7 cases per month, the study statistician will recommend to the RTOG DMC that the study be terminated.

13.4 Analysis Plan (3/13/08)

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

13.4.1 *Primary Endpoint* **(6/17/08)**

The primary endpoint is freedom from any bone fracture (FABF). The time of failure will be measured from the date of randomization to the date of documented bone fractures, defined as any fracture of the bone. The FABF function will be estimated by the Kaplan-Meier method.[82] The null and alternative hypotheses are:

$$H_0: FABF_{Control}(t) \geq FABF_{Zometa®}(t)$$
$$H_A: FABF_{Control}(t) < FABF_{Zometa®}(t)$$

where t is time and $FABF_{Control}$ and $FABF_{Zometa®}$ are the freedom from any bone fracture for the control and Zometa® arms, respectively.

The log-rank test will be used to test the primary hypothesis[83] with a significance level of 0.0496 at the final analysis when everyone has been followed for three years. In addition, unadjusted and adjusted hazard ratios and the respective 95% confidence intervals will be computed using the Cox proportional hazards regression model.[84] DXA Scan T Score of the Hip, duration of LHRH therapy and other baseline factors as appropriate will be adjusted in this analysis.

13.4.2 *Secondary Endpoints*

13.4.2.1 *Percent Change in Bone Mineral Density (BMD) at Three Years*

The percent change in bone mineral density (BMD) is defined as the percentage change in BMD from baseline to 3 years computed for each case by the following formula:

$$\%Change\ BMD = (BMD_{3\ years} - BMD_{Baseline}) / BMD_{Baseline} * 100$$

The null and alternative hypotheses are:

$$H_0: \mu_{\%Change\ BMD,\ Control} \geq \mu_{\%Change\ BMD,Zometa®}$$
$$H_A: \mu_{\%Change\ BMD,\ Control} < \mu_{\%Change\ BMD,Zometa®}$$

The two-sample t-test assuming equal variances will be used to test the hypothesis with a significance level of 0.05 and when everyone has been followed for 3 years. Because bone density data varies by manufacturer, the standardized BMD will be calculated using the conversion equations[85] for the different manufacturers.

13.4.2.2 *Quality of Life Measured by the FACT-G*

The primary patient-reported endpoint for the FACT-Q 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) using all assessments as described in Section 13.2.3.2 from baseline (i.e., pre-treatment) to 3 years 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.[86] 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 of 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 (DXA scan T score and duration of LHRH therapy). 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 independent of the missing data given the observed data. A graphical method at a minimum will be 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 method[87] 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 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 mechanism[88] 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 **A**rea **U**nder The **C**urve (AUC) analysis will also be done using all FACT-G subscales and total score assessments from baseline to 3 years from start of protocol treatment for each patient. A two-sample t-test with a Bonferroni-adjusted one-sided $\alpha = 0.05/5$, to control the overall type I error rate for testing multiple domains, will be used to test the null hypothesis that the mean AUC of the Zometa® arm is less than or the same as the control arm versus the alternative that the Zometa® arm is greater than the control arm.

13.4.2.3 *Utility (as measured by the EQ-5D) of the Use of Bisphosphonates*:
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 3 years 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 of quality (qi) of K health states times the duration (si) spent in each health state.

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

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 and Futility* **(6/17/08)**
One interim treatment comparison will be performed for efficacy of the experimental treatment using Haybittle-Peto boundaries. At the planned interim analysis, the following hypothesis for the primary endpoint will be tested with a nominal significance level, as shown in Table 2.

H_0: $FABF_{Control}$ (t) ≥ $FABF_{Zometa®}$ (t)
H_A: $FABF_{Control}$ (t) < $FABF_{Zometa®}$ (t)
where t is time and $FABF_{Control}$ and $FABF_{Zometa®}$ are the freedom from any bone fracture for the control and Zometa® arms, respectively.

At the planned interim analysis, the p-value from the 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 bone fractures (any bone fracture) 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 FABF rate of the Zometa® arm is higher than the control arm (reject the null hypothesis, H_0). Otherwise, we will continue the trial.

Table 2: Nominal Significance Levels (α_n) for the Interim Analysis

Time of Interim Analysis	Nominal Significance Level
Number of Any Bone Fractures	**Reject H_0 if p-value $\leq \alpha_{n1}$**
33	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 combined over treatment arms.

The study statistician will report any problems identified to the study chairs, RTOG CCOP 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 clinically meaningful improvement in the probability of remaining free of any bone fracture, defined as any fracture of the bone at 3 years in patients receiving Zometa® compared to that of patients receiving standard treatment. The analysis reporting the treatment results will be carried out after 101 bone fractures (any fracture) have been observed, unless the criteria for early stopping are met. The FABF difference between the control arm and the experimental arm (Zometa®) will be tested using the log-rank test at a significance level of 0.0496 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, DXA Scan T Score and duration of LHRH therapy, will be used for exploratory analyses of treatment comparisons. Also, where feasible, treatment comparisons with respect to all endpoints will be compared within each ethnic and racial category.

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 9202 and 9413, the projected accrual by gender and race/ethnicity is shown in the Table 3.

Table 3: Planned Gender and Minority Inclusion

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	N/A	38	38
Not Hispanic or Latino	N/A	1234	1234
Ethnic Category: Total of all subjects*	N/A	1272	**1272**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	N/A	1	1
Asian	N/A	7	7
Black or African American	N/A	217	217
Native Hawaiian or other Pacific Islander	N/A	5	5
White	N/A	1042	1042
Racial Category: Total of all subjects*	N/A	1272	**1272**

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APPENDIX I (8/16/07) (3/13/08) (6/17/08)

RTOG 0518

Informed Consent Template for Cancer Treatment Trials (English Language)

A Phase III Randomized Trial to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced 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 prostate cancer and as part of your treatment, you are receiving radiation therapy and hormone therapy.

Why is this study being done?

Hormone therapy can help to control prostate cancer, but it also can cause bone fractures (breaks). These breaks are a result of weak bones.

The purpose of this study is to compare the effects, good and/or bad, of a drug, zoledronic acid (Zometa®), plus vitamin D and a calcium supplement, with vitamin D and a calcium supplement alone. Zoledronic acid is a drug given through the vein to strengthen bones.

The study is being done to find out if zoledronic acid prevents bone fractures by strengthening bones better than vitamin D and calcium alone. In this study, you will get zoledronic acid plus vitamin D and a calcium supplement or vitamin D and a calcium supplement alone. You will not get both.

As part of this study, you will have a test called a dual x-ray absorptiometry (DXA) scan to help the study doctor determine the strength of your bones. Readings from the DXA scan are called “T” scores. A T score of ≥ -1.0 is normal. A T score of < -1.0 means the bone is “softening”, also known as osteopenia. T scores of ≤ -2.5 mean weak bones or osteoporosis. You will have this test three times in this study: before you begin the study, at 18 months from the start of treatment, and at the end of treatment (3 years).

How many people will take part in the study?

About 1, 272 people will take part in this study.

What will happen if I take part in this research study? (6/17/08)

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 weighed and asked about your ability to carry out your daily activities.
- Your teeth, gums, and chewing ability will be evaluated, and you will be asked about any dental surgery you may have had in the past.
- A DXA scan (a dual x-ray absorptiometry [DXA] scan)
- X-rays of your spine
- A bone scan, a type of x-ray to find out if cancer has spread to your bones
- Blood tests for kidney function and calcium levels in your blood

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** each time you receive zoledronic acid plus vitamin D and a calcium supplement, **or** vitamin D and a calcium supplement alone (every 6 months). They are part of regular cancer care.

- A physical exam
- You will be weighed and asked about your ability to carry out your daily activities.
- Blood tests for kidney function and calcium levels in your blood to determine the amount of zoledronic acid (if you are in Group 1) you should receive.

At 18 months from the start of treatment, you will have a physical exam and a DXA scan.

All patients in this study will receive radiation therapy while they receive zoledronic acid plus vitamin D and a calcium supplement, or vitamin D and a calcium supplement alone. Your doctor will discuss the choice of external radiation therapy or internal radiation therapy (brachytherapy) with you. External radiation therapy for prostate cancer is usually given once a day, five days a week for 8 weeks. A typical external radiation treatment lasts about 15 minutes. Internal radiation therapy involves the insertion of a temporary or permanent implant into your body, and radiation therapy is given by means of the implant. A typical brachytherapy treatment for prostate cancer takes 5-30 minutes, and usually a total of 2 treatments are given within a 24 hour period. **(8/16/07)**

In addition, all patients in this study will receive one of the commercial hormone treatments currently being used for prostate cancer while they receive zoledronic acid plus vitamin D and a calcium supplement, or vitamin D and a calcium supplement alone. Your doctor will discuss the choice of hormone treatments with you. Hormone treatments are given in various ways, such as by injection. Your doctor will discuss with you how you will receive hormone treatments.

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 doctor can choose the group you will be in. 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 zoledronic acid through your vein every 6 months for 3 years (6 infusions). Each infusion takes about 15 minutes. You also will take vitamin D (1 pill) and a calcium supplement (1 pill) by mouth daily for 3 years.

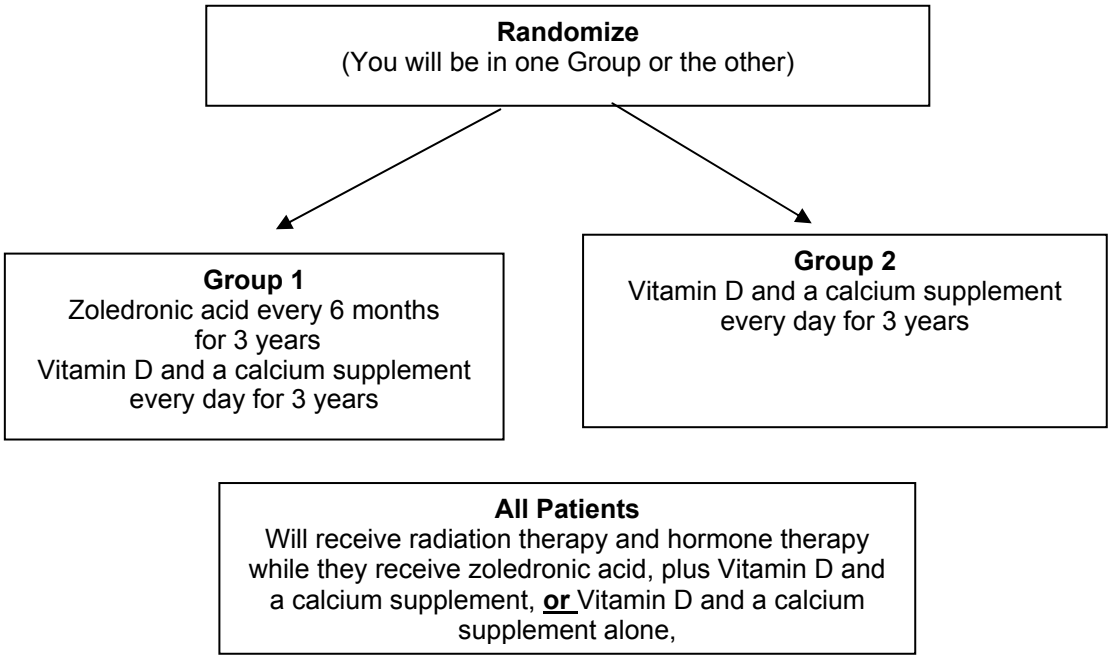
If you are in Group 2 (often called "Arm B"), you will take vitamin D (1 pill) and a calcium supplement (1 pill) by mouth daily for 3 years.

In year 3, you will have the following tests or procedures:

- A physical exam
- You will be weighed and asked about your ability to carry out your daily activities.
- You will be asked about any dental surgery you may have had in the past.
- A DXA scan
- X-rays of your spine

Study Plan (11/17/06) (6/17/08)

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?

You will receive treatment and will be seen every 6 months for 3 years.

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, vitamin D, and calcium supplement can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup 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, doctors 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 radiation therapy, hormone therapy and zoledronic acid. 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 and Side Effects Related to External Radiation Therapy

Very Likely

- Tanning or redness of skin in treatment area
- Rash, itching, or peeling of skin
- Temporary hair loss in the treatment area
- Tiredness, which is temporary
- Nausea, which is temporary
- Diarrhea, which is temporary
- Stomach cramps
- Bladder irritation
- Infertility (the inability to father children), which is permanent

Less Likely, But Serious (6/17/08)

- Injury to the bladder
- Injury to the urethra, the tube that carries urine from the bladder and semen from the sex glands to the outside of the body
- Injury to the bowel or other tissues in the pelvis or abdomen, which could result in surgery
- Rectal bleeding
- Rectal urgency or loss of rectal control
- Urinary tract infection
- Urgency and/or painful urination
- Loss of bladder control, which may be permanent
- Blockage of the intestinal or urinary tract
- Impotence or failure to achieve an erection, which may be permanent

Risks Related to Internal Radiation Therapy (Brachytherapy)

Very Likely

- Infection that may need to be treated with antibiotics
- Soreness in the implant area
- Tiredness, which is temporary
- Nausea, which is temporary
- Diarrhea, which is temporary
- Stomach cramps
- Bladder irritation with some bleeding
- Urinary tract infection
- Urgency and/or painful urination
- Impotence or failure to achieve an erection, which may be permanent
- Infertility (the inability to father children), which is permanent

Less Likely, But Serious (6/17/08)

- Injury to the bladder
- Injury to the urethra, the tube that carries urine from the bladder and semen from the sex glands to the outside of the body
- Injury to the bowel or other tissues in the pelvis or abdomen, which could result in surgery
- Rectal bleeding
- Blockage of the intestinal or urinary tract

- Loss of bladder control, which may be permanent
- Serious infection

Risks Related to Hormone Therapy

Likely
- Hot flashes or sweating episodes
- Weight gain
- Loss of libido or interest in sex, which may be permanent
- Impotence or failure to achieve an erection, which may be permanent

Less Likely
- Allergic reaction at injection site
- Changes in the texture of your hair
- Feelings of depression or other emotional changes
- Breast swelling or tenderness
- Unusual taste in the mouth
- Increased thirst and urination
- Skin redness or hives
- Nausea
- Vomiting
- Diarrhea
- Dizziness
- Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
- Blood clots
- Loss of bone density
- Bone pain
- Loss of strength
- Loss of the amount of muscle you have (muscle mass)
- Loss of penis length
- Decrease in the size of your testicles
- Increased cholesterol
- High blood pressure
- Worsening of diabetes (high blood sugar)

Rare but Serious
- Allergic generalized rash
- Difficulty breathing

Risks Related to Zoledronic Acid (Zometa®) [3/22/07]

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 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 (6/17/08)
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 father a baby while receiving treatment on this study because the radiation therapy and drugs you will be taking can affect an unborn baby. If you are able to father a child, you must agree to use adequate birth control during treatment and for at least 3 months afterwards. Check with your study doctor about what kind of birth control methods to use. Some methods might not be approved for use in this study. Radiation therapy for prostate cancer results in permanent infertility (you will not be able to father children).

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 doctors hope that zoledronic acid will prevent bone fractures (breaks), there is no proof of this yet. We do know that the information from this study will help doctors learn more about zoledronic acid as a treatment for this side effect of cancer treatment. 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 weak bones or fractures without being in a study
- Taking part in another study

- Getting no treatment for weak bones or fractures

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

Will my medical information be kept private?

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)

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). 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 will supply the vitamin D and calcium supplements at no cost to you.

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 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 meeting regularly to monitor safety and other data related to this study. The Board may receive confidential patient information, but they will not receive your name 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 studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Quality of Life Study

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 also looks at how you are able to carry out your day-to-day activities.

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.

One of the questionnaires requires data from Medicare on reimbursement amounts. If your health care is covered at least in part by Medicare, you will be asked to provide your social security number. Your social security number will not be used for any other purposes. We will do our best to make sure that your personal information is kept private; the chance that this information will be given to someone else is very small.

You will be asked to complete 2 questionnaires on your first visit and every 6 months for 3 years. 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 2 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 two 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

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry 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).

APPENDIX III

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DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable or visible by imaging
- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)

T2 Tumor confined with prostate*
- T2a Tumor involves one-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3, but as T2.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Primary Tumor, Pathologic (pT)

pT2* Organ confined
- pT2a Unilateral, involving one-half of one lobe or less
- pT2b Unilateral, involving more than one-half of one lobe but not both lobes
- pT2c Bilateral disease

pT3 Extraprostatic extension
- pT3a Extraprostatic extension**
- pT3b Seminal vesicle invasion

pT4 Invasion of bladder, rectum

*Note: There is no pathologic T1 classification

**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

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Distant Metastasis (M)*

MX	Presence of distant metastasis cannot be assessed (not evaluated by any modality)	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Nonregional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

Histopathologic Grade (G)

GX	Grade cannot be assessed
G1	Well-differentiated (slight anaplasia [Gleason 2-4])
G2	Moderately differentiated (moderate anaplasia [Gleason 5-6])
G3-4	Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

Stage Grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2, G3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	N0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

APPENDIX IV

RTOG 0518, 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. **U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) and fax it 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.

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.

NOTE: The SASF for this study is available on the RTOG web site, http://www.rtog.org, next to the protocol.