A Randomized Clinical Trial of Prophylactic Risedronate for Patients with Peripheral Lung Tumors Treated with SBRT
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC 99518

ClinicalTrials.gov: NCT03861091

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| **Principal Investigator:** | *Name and Title* | Michael Farris, M.D. |
| | *Department / Section Name* | Radiation Oncology |
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| **Biostatistician:** | *Name and Title* | Beverly Levine, Ph.D. |
| | *Department / Section Name* | Biostatistics Core |
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| **Study Coordinators:** | *Name and Title* | Sheri Whittington |
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| **Regulatory Contact:** | *Name and Title* | Cindy Miller, AAS |
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**Participating Institution(s):**
Wake Forest Baptist Comprehensive Cancer Center
---High Point Regional Medical Center (part of WFBH)

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**Confidential:**

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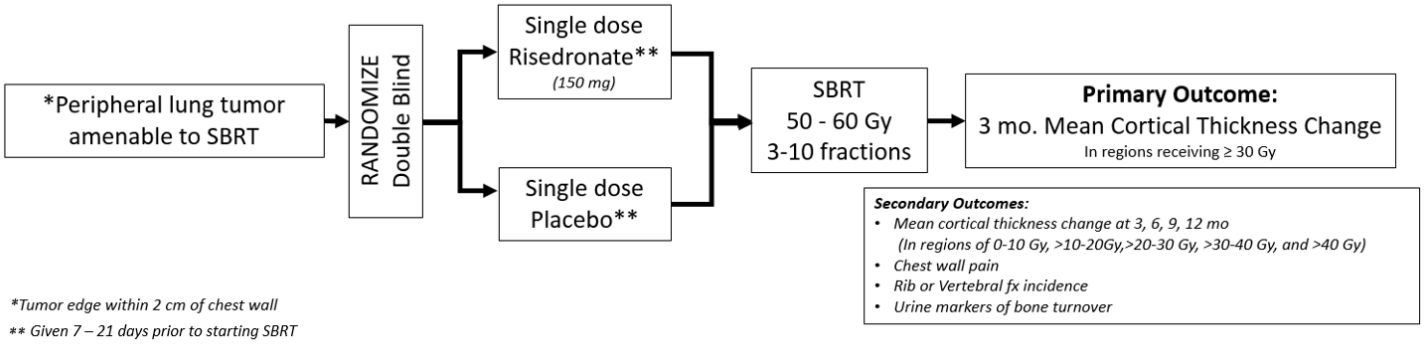
# SCHEMA




*Tumor edge within 2 cm of chest wall

** Given 7 – 21 days prior to starting SBRT

# 1.0 Introduction and Background

## 1.1 Synopsis

Approximately half of the 1.7 million new cancer diagnoses annually will be treated with ionizing radiation therapy (RT). Improvements in screening and treatment continue to decrease mortality. As a result, long term sequelae of therapy have become a major concern[1-3].

Thoracic stereotactic body radiation therapy (SBRT) for the treatment of primary or metastatic lung tumors near the chest wall unavoidably delivers high doses of radiation to the surrounding normal ribs or vertebrae and can predispose patients to significant chest wall pain (CWP), radiation induced rib fractures (RIRF) or even vertebral fractures[4-6]. Rates of toxicity have been correlated with dose received by the chest wall. On average, around 35% of patients develop grade 3 or higher CWP when greater than 30 cc of chest wall receives 30 Gy or more[7].

In clinical practice this is a very common scenario and a difficult dosimetric constraint to achieve. The incidence of rib fractures within the first year of treatment has been reported as high as 40%[6,8-13]. Patients can experience severe pain, compromised ventilation, and impaired quality of life. In the elderly, decreased oxygen saturation as a result of compromised ventilation can reduce life expectancy [14]. Radiation related bone injury is not limited to the ribs and SBRT however. Rather, it is a source or morbidity at multiple skeletal locations. The five year post-RT pelvic fracture rate is ~30% in women treated for the most common gynecologic malignancy, endometrial adenocarcinoma[15,16]. Likewise, hazard ratios for RT induced hip and femoral neck fracture indicate significant increased risk at five years post-RT for cervical (1.66), rectal (1.65), and anal (3.16) cancers[17]. Alarmingly, the rate of incomplete healing is high with RT-induced fractures, which greatly contributes to morbidity[18,19]. Therefore, RT-induced bone damage is a persistent and major source of functional impairment, pain, and mortality in many cancer survivors.

The exact mechanisms of RT-induced bone damage are unclear. Historically, persistent damage to osteoblasts was thought to play a role by lowering bone formation and bone mineral density over time[20-23]. However, we recently discovered that local RT rapidly increases the number and activity of osteoclasts in rodents [24], and we have shown this burst of osteoclast activity causes substantial early bone loss[22]. This is now well-accepted[25-32]. By suppressing osteoclast activity during RT using an antiresorptive bisphosphonate, risedronate, we prevented this rapid bone loss in rodents[22]. This is illustrated in Fig. 1 and Fig. 2. Suppressing early osteoclast activity is an appealing therapeutic approach for preventing RT-induced fractures. A variety of urinary biomarkers have been linked to increased osteoclastic activity in osteoporotic populations, and the most frequently tested marker is urinary NTX N-telopeptide. [33]. These biomarkers have been assessed following radiation to the pelvis with or without bisphosponates and were shown to decrease with the addition of bisphosphonates[34].

We have devised a novel 3D mapping approach which utilizes DICOM computed tomography (CT) images and allows us to visualize and quantify the changes in bone cortical thickness (C.Th) following RT and associate bone changes with RT dose distribution. (Fig. 3) Furthermore, we illustrated dose-dependent cortical thinning to the exact sites of eventual fracture in patients receiving lung SBRT near the chest wall, as well as bone loss to discrete, weight-bearing sub-regions of the femoral neck after RT for pelvic cancers[4,35]. In areas of the ribs receiving > 30 Gy approximately 92% of treated patients developed significant cortical thinning by 3 months, and 2 patients developed rib fractures by as early as 6 months[33]. Using this mapping technique, we have also illustrated significant and persistent cortical thickness changes as early as 2 months post treatment in the treated vertebrae of nonhuman primates receiving single fraction high dose chest RT (Fig. 4)[36].

*Clinical relevance*

On review of treatment planning records over the last month in our department, we have treated 18 patients who would have qualified for inclusion on this study. This is a reasonable representation of our average SBRT treatment population. More than 2/3 of our SBRT plans unavoidably exceed standardized dosimetry constraints for the ribs/chest wall, and roughly 30-40% of our patient population complains of chest wall pain requiring narcotics/analgesics after SBRT. Typically this occurs within 3 - 8 months. This presents clinicians with a difficult decision to either compromise on effective tumor dose by reducing the dose per fraction, or accept a higher risk of chest wall toxicity with more intensive fractionations proven to have better local tumor control.

*Conclusions:*

We aim to determine if single dose prophylactic suppression of early RT induced osteoclast activity with bisphosphonates diminishes or prevents RT induced cortical bone thinning, fracture, and pain.

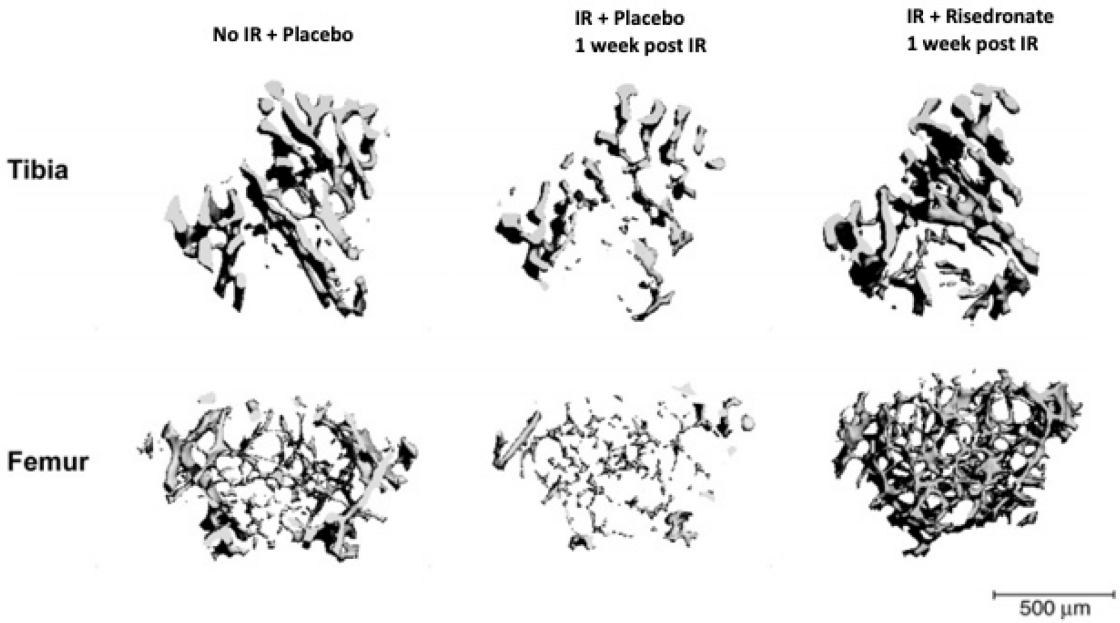



**Figure 1.** MicroCT images are shown of trabecular bone in the proximal tibial metaphysis (Tibia) and distal femoral metaphysis (Femur) from mice that were non-irradiated (No IR) and those who were irradiated (IR) then sacrificed 1 week later. In the irradiated mice, a 2 Gy dose of x-rays was administered with a PBS placebo injected subcutaneously (IR+ Placebo) or with subcutaneous risedronate injections (IR+ Risedronate).

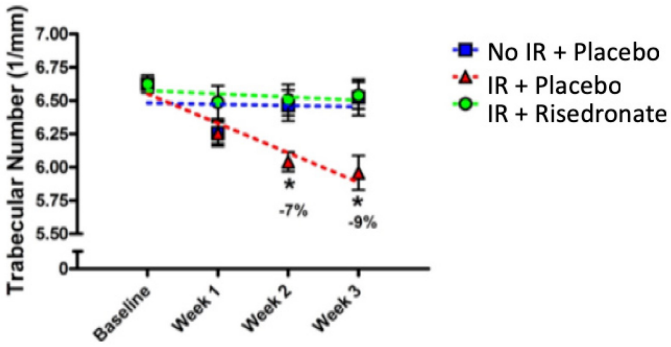


**Figure 2.** Trabecular number vs time in mice. The blue boxes represent mice that were not irradiated and were given a PBS placebo injected subcutaneously (No IR +Placebo), while the red triangles and green circles represent mice that received a 2 Gy dose of x-rays was administered with a PBS placebo injected subcutaneously (IR+ Placebo) or with subcutaneous risedronate injections (IR+ Risedronate).

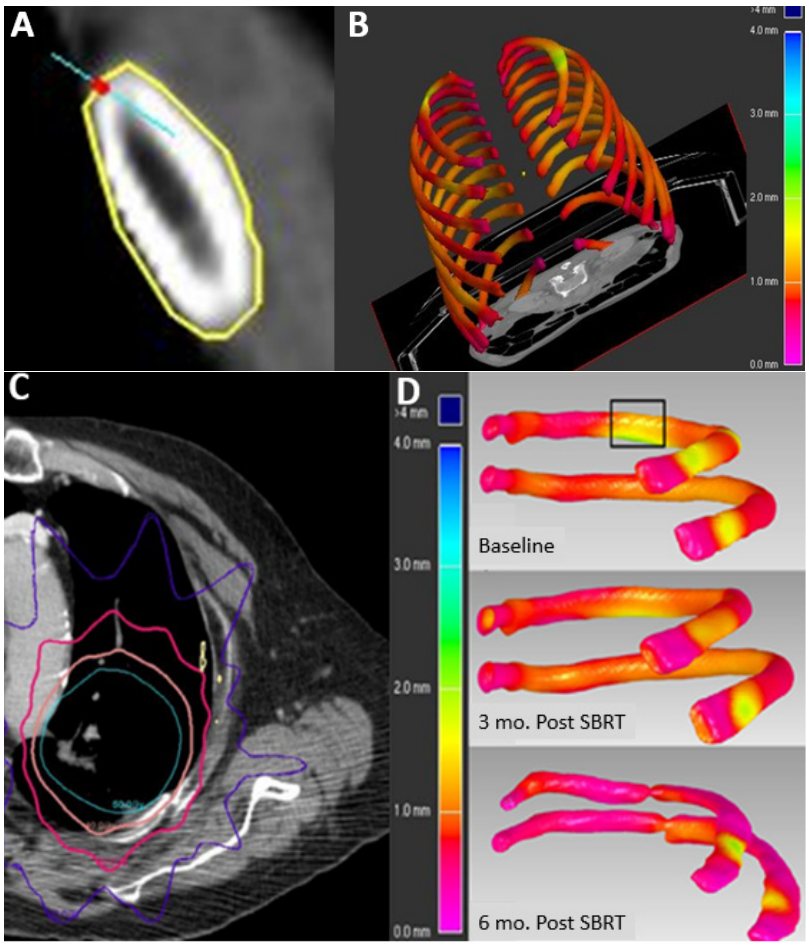



**Figure 3.** A) Illustration of cortical thickness vector measurement for a rib. (B) This is performed thousands of times on each CT scan to create cortical thickness maps for all ribs with a color scale corresponding to thickness in millimeters. (C) Radiation dose is associated with locations showing rib thinning. (D) Cortical thinning and subsequent rib fracture is visually evident at 3 and 6 months post SBRT in an area of chest wall that received nearly the tumor prescription dose (square box).

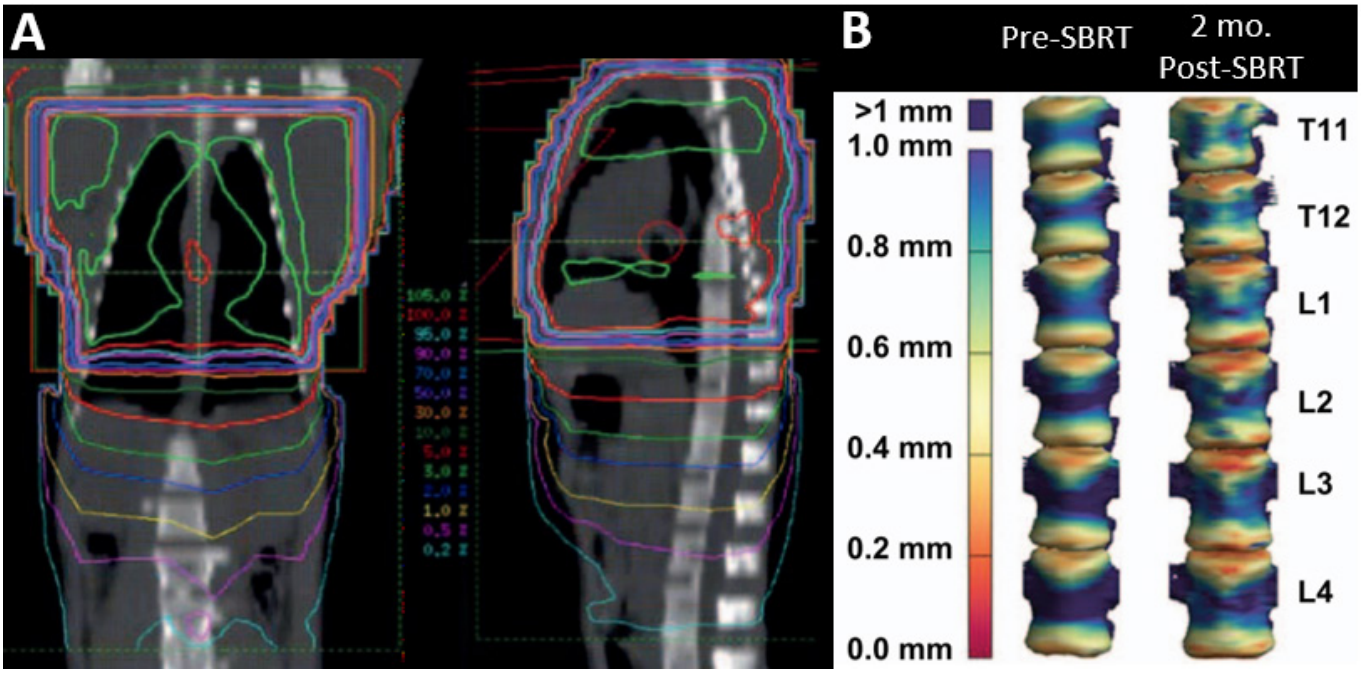



**Figure 4.** A) Non-human primate rhesus monkeys received a single fraction 10 Gy to the whole chest, and isodose curves illustrating radiation dose distribution are shown. B) Cortical thickness maps illustrated dose dependent cortical thickness loss at 2 months post radiation.

## 1.2 Risedronate Background Information

Much of the following detailed information below was obtained from the product monograph from Allegran Pharma Co. Markham, Ontario L6G0B5 August 2017, Submission Control 205107. In some instances, this information was directly reproduced from the product monograph.

Background information on the study agent:
ACTONEL® (risedronate sodium hemi-pentahydrate) is a commonly used bisphosphonate medication that is FDA approved for the indications below.

- Treatment and prevention of osteoporosis in postmenopausal women
- Treatment of osteoporosis in men, to improve bone mineral density
- Treatment and prevention of glucocorticoid-induced osteoporosis in men and women
- Paget's disease of bone

Clinical studies and use with radiation
Risedronate has been utilized in multiple large prospective clinical trials and was shown to significantly reduce vertebral fracture incidence in patients with low bone mass and vertebral fractures, regardless of age, years since menopause or disease severity at baseline. A North American trial illustrated a significant reduction in the 1-year rate of new vertebral fractures by 65% compared to placebo. Similarly, a multinational trial also illustrated a 61% reduction in the 1-year rate of new vertebral fractures.
There are no contraindications to concurrent use of risedronate and chest external beam radiation. Bisphosphonates are not routinely discontinued during SBRT for lung tumors. There is a known risk of jaw osteonecrosis that may occur following dental surgery or spontaneously with bisphosphonates, however this is not a reported finding in the ribs. Osteoradionecrosis in the jaw is a separate process

that can occur when treating head and neck cancers without bisphosponates and is a result of poor vasculature in the mandible. In the setting of head and neck cancer treatment with radiotherapy, we would discontinue bisphosphonates, however this is not extrapolated to other parts of the body when receiving radiotherapy while on bisphosphonates

Clinical studies have been performed with concurrent use of bisphosphonates and radiation therapy in the pelvis without excess toxicity. Choo et al, conducted a randomized trial in patients with prostate cancer receiving placebo or risedronate concurrently with external beam radiation and androgen deprivation therapy[37]. They illustrated prevention of bone mineral density (BMD) loss at 2 years and significant suppression of bone turnover biomarkers in patients receiving risedronate. There were no excess or unexpected toxicities due to concurrent risedronate and RT.

Simiarly, Gierloff et al. illustrated that the addition of zolendronate with radiation in patients with metastatic bone disease, prevented early radiation induced bone collagen degradation when compared to placebo[34]. There was significant reduction in urine excretion markers of degradation including hydroxylysylpyridinoline and lysylpyridinoline. Again, no excess toxicity was noted with the concurrent use of bisphosphonates and radiation.

Pharmacokinetics:

**Summary of Pharmacokinetic Parameters of Risedronate**

| | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $t_{1/2}$,z (h) | $AUC_{0-\infty}$ (ng·h/mL) | Clearance (L/h/kg) | $V_z$ (L/kg) |
|---|---|---|---|---|---|---|
| 5 mg tablet; single dose | 0.85 | 0.93[a] | 206.1 | 3.45 | 19.94 | 5542 |
| 30 mg tablet; single dose | 4.2 | 0.87[a] | 226.1 | 17.1 | 23.60 | 7542 |
| 35 mg tablet; multiple dose[b], steady state | 10.6 | 0.49 | nd | 53.3 | 12.9 | nd |
| 35 mg DR tablet; single dose | 14.1 | 3.0[d] | nd | 34.2[e] | nd | nd |
| 150 mg tablet, single dose | 74.8[d] | 0.66[d] | 349.6[d] | 332.4[d] | 6.94[d] | 3118[d] |

[a]: arithmetic mean; [b]: administered weekly; [c]: administered on two consecutive days per month (150 mg total monthly dose); [d]: geometric mean; $t_{1/2}$, z: is the half-life of the terminal exponential phase; $V_Z$: is the terminal volume of distribution uncorrected for bioavailability; nd: not determined; [e] AUCtlast.

Drug Interactions:
No specific drug-drug interaction studies were performed with risedronate sodium film-coated tablets. Animal studies have demonstrated that risedronate is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected systemically or in bone. The binding of risedronate to plasma proteins in humans is low (24%), resulting in minimal potential for interference with the binding of other drugs. In an additional animal study, there was also no evidence of hepatic microsomal enzyme induction. In summary, risedronate sodium is not systemically metabolized, does not induce cytochrome P450 enzymes and has low protein binding. Risedronate sodium is therefore not expected to interact with other drugs based on the effects of protein binding displacement, enzyme induction or metabolism of other drugs. In vitro studies suggest that the amount of EDTA contained in the ACTONEL DR formulation (approximately 1.5 mM) will not significantly affect aqueous solubility of antivirals (nelfinavir, lamivudine, emtricitabin) and drugs with a narrow therapeutic index (digoxin, lithium carbonate, potassium chloride). Thus, co-administration with ACTONEL DR is not likely to alter their absorption.

Patients in clinical trials were exposed to a wide variety of commonly used concomitant medications (including NSAIDs, H2-blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants, cardiac glycosides). While there was no apparent evidence of clinically relevant interactions in the clinical trials, such interactions cannot be ruled out on the basis on these data.

Metabolism:
There is no evidence that risedronate is systemically metabolized.

Route of elimination:
Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an intravenous dose is recovered in the urine over 28 days. The mean renal clearance is 105 mL/min (CV = 34%) and mean total clearance is 122 mL/min (CV = 19%), with the difference primarily reflecting non-renal clearance or clearance due to adsorption to bone. The renal clearance is not concentration dependent, and there is a linear relationship between renal clearance and creatinine clearance. Unabsorbed drug is eliminated unchanged in feces. Once risedronate is absorbed, the serum concentration-time profile is multi-phasic with an initial halflife of about 1.5 hours and a terminal exponential half-life of 480 hours. Although the elimination rate of bisphosphonates from human bone is unknown, the 480 hour half-life is hypothesized to represent the dissociation of risedronate from the surface of bone.

Special Populations and Conditions
Pediatrics: Risedronate pharmacokinetics have not been studied in patients < 18 years of age.
Geriatrics: Bioavailability and disposition are similar in elderly (> 65 years of age) and younger subjects. No dosage adjustment is necessary.
Gender: Bioavailability/disposition following oral administration are similar in men and women.

# 2.0 Objectives

This is a double blind randomized controlled study investigating the efficacy of a single dose of 150 mg risedronate (a bone anti-resorptive) vs a single dose of placebo given prior to SBRT for peripheral lung tumors that are within 2 cm of the chest wall. Our hypothesis is that the use of a single dose of 150 mg risedronate will eliminate or greatly reduce the rapid bone loss that occurs with radiation induced early osteoclast recruitment/activation.

Patients will be given either a single dose of 150 mg risedronate or placebo at the time of their treatment mapping “simulation” CT scan or within 7-21 days of the start of SBRT. Typically, radiation treatments begin at 1 – 3 weeks following this mapping scan, as each treatment plan requires detailed physics calculations and quality assurance checks.

All CT imaging referenced below is performed as a routine standard of care surveillance and is necessary for cancer treatment follow-up. These chest CT scans that are utilized in this research protocol would be performed every 3 months regardless of inclusion on this trial.

## 2.1 Primary Objective(s)

2.1.1 The primary objective is to assess the percent change in bone mean cortical thickness within regions of bone receiving 30 Gy or more at 3 months after SBRT. The % change

in mean cortical thickness will be compared between patients who received risedronate and those who received placebo.

## 2.2 Secondary Objective(s)

2.2.1 In addition to the primary objective, we will further analyze the remaining routine follow-up chest CT scans, for mean cortical thickness change in regions of bone that received 0 – 10 Gy, >10 – 20 Gy, > 20 – 30 Gy, > 30 – 40 Gy, and > 40 Gy at all time points including 3 months, 6 months, 9 months, and 12 months. These scans are standard of care and would be performed regardless of inclusion on this trial. This will allow us to determine the potential persistence of effects from SBRT and bisphosphonate use.

2.2.2 We will assess and compare the incidence and grade (per modified CTCAE v.5) of radiation induced chest wall pain within the radiation treatment portal (within the 50% isodose line) at time of each routine follow up visit (3 months, 6 months, 9 months, and 12 months post SBRT). The purpose of utilizing a placebo and double-blind design is that chest wall pain is a subjective finding. Furthermore, it is unclear if chest wall pain from radiation is directly due to bone damage, nerve damage, muscle irritation, or a combination of all of these factors. The use of placebo will help us reduce the potential for bias in pain assessment.

2.2.3 We will assess and compare the incidence of rib and vertebral fractures (as noted on CT imaging) that occur within 12 months of irradiation and are within the radiation treatment field. The radiation treatment field will be defined as within the 50% isodose line.

2.2.4 The urine concentration of an osteoclast-specific biomarker, urinary N-telopeptide (NTX) indicating osteoclast activity will be assessed prior to SBRT and at each routine follow up visit (at 3 months, 6 months, 9 months, and 12 months post SBRT).

## 2.3 Exploratory Objectives

2.3.1 We will analyze novel anatomic dosimetric substructures on already completed radiation plans such as rib neurovascular bundles. These anatomical structures will be contoured onto the stored planning CT scans and the raystation planning system will allow us to calculate the dose that these structures received. We will assess the relation between this calculated dose and development of/grade of chest wall pain during follow-up. The standard structure that is routinely contoured for these cases is a crude rind encompassing 2-3 cm of the entire chest wall. We are hypothesizing that dose to specific substructures in the chest wall may be more useful in the prediction of chest wall pain development.

2.3.2 If funding permits, we will analyze, and compare between groups, the urine concentration of markers of bone turnover activity. These will all be assessed prior to SBRT and at the 6 month follow up visit post SBRT.

2.3.3 We will analyze and compare between groups the urine concentrations of pain-associated cytokines prior to SBRT and at the 6 month follow up visit post SBRT. Also, if funding permits, the urine concentration of pain-related neurotrophic growth factors (proNGF, proBDNF, GDNF), and neuropeptides (CGRP and Substance P) will be measured.

# 3.0 Patient Selection

Biopsy is not required for enrollment.
The lung tumor may be a lung primary tumor or a metastatic tumor to the lung.
Prior radiation to any part of the body including the lungs, breast, or thorax is permitted.

## 3.1 Inclusion Criteria

3.1.1 Patients must be 18 years or older, but there is no upper limit on age of inclusion.

3.1.2 Patients must have a peripheral lung tumor that is amenable to SBRT as determined by the treating radiation oncologist. To be classified as a peripheral lung tumor, the tumor edge (the edge of the gross tumor volume or GTV in radiation treatment planning software) must be within 2 cm of the chest wall. This is determined by the treating radiation oncologist. The chest wall is defined as the chest wall musculature or ribs/vertebrae immediately adjacent to the lungs.

3.1.3 Patients must have ECOG status of 0-3

3.1.4 Patients must have a life expectancy of at least 3 months as determined by the treating radiation oncologist.

3.1.5 Patients must have the ability to understand and the willingness to sign an IRB-approved informed consent document.

## 3.2 Exclusion Criteria

Prior radiation to any part of the body including the lungs or thorax is not an exclusion criteria

3.2.1 Tumor edge is greater than 2 cm from the chest wall. The edge of tumor is the edge of the gross tumor volume or GTV as defined in radiation treatment planning software. This is determined by the treating radiation oncologist.

3.2.2 Tumors that are expected to require more than 10 fractions of radiation as determined by the treating radiation oncologist.

3.2.3 History of using bone anti-resorptive agents including bisphosphonates or RANK-L inhibitors within the last 1 year.

3.2.4 Inability to stand or sit upright for at least 30 minutes, which is necessary for ingestion of risedronate.

3.2.5 Hypocalcemia defined as serum total calcium lower than 8.5 mg/dL on most recent bloodwork that is within 3 months of administration of study drug/placebo

3.2.6 Severe renal impairment (EGFR <30 mL/min) on most recent bloodwork that is within 3 months of administration of study drug/placebo

3.2.7 Known allergy to risedronate or other bisphosphonates

3.2.8 Surgery affecting the bone or dental operations within the last 6 months
***This will be explicitly asked and documented in the EMR by treating radiation oncologist**
3.2.8.1 Dental operations do not include routine cleaning or cavity fillings
3.2.8.2 Dental operations that exclude patients refer to any manipulation of mandible.

3.2.9 Positive urine pregnancy test in women of child bearing potential within 1 week of registration. Pregnant women are excluded from this study because radiation has clear teratogenic and potentially abortifacient risks.

## 3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study. The study consent form will also be provided in Spanish for Spanish-speaking participants.

Based on WFBCCC population estimates, we may expect approximately 44% of participants to be women. Translating this to our sample size estimate of 84 patients, we may enroll approximately 42 women. We may enroll approximately 10-13% Black or African American patients. Based on our catchment area and hospital demographics we do not expect high accruals of individuals of Hispanic/ Latino, American Indian/Alaska Native or Asian ancestry; however, no individual will be excluded from the study if they satisfy the above inclusion/exclusion criteria. Should we not meet or exceed these estimates, the PI will engage the Office of Cancer Health Equity to discuss strategies to enhance recruitment in these target populations.

# 4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment. You must perform the following steps in order to ensure prompt registration of your patient:

1.0 Complete the Eligibility Checklist (Appendix A)
2.0 Complete the Protocol Registration Form (Appendix B)
3.0 Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

Contact Information:
Protocol Registrar PHONE (336) 713-6767
Protocol Registrar FAX (336) 713-6772
Protocol Registrar E-MAIL (registra@wakehealth.edu)

*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4.0 Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.
To complete the registration process, the Registrar will:

- assign a patient study number
- randomize the patient
- other appropriate actions
- register the patient on the study

# 5.0 Study Outcomes and Study Measures

All CT imaging referenced below is performed as a routine standard of care and necessary for cancer treatment follow-up. These chest CT scans utilized in this research protocol would be performed every 3 months regardless of inclusion on this trial.

## 5.1 Primary Outcome

5.1.1 The primary outcome measure is the percent change in mean cortical thickness (C.Th) of bones receiving 30 Gy or more at 3 months post SBRT, when compared to pre-SBRT cortical thickness

## 5.2 Secondary Outcomes

5.2.1 The change in mean C.Th of bones will be assessed in regions of bone that received 0 – 10 Gy, >10 – 20 Gy, > 20 – 30 Gy, > 30 – 40 Gy, and > 40 Gy at all time points including 3 months, 6 months, 9 months, and 12 months.

5.2.2 Chest wall pain incidence and grade will be collected as per modified CTCAE v. 5 within the within the 50% isodose line. Appendix K

5.2.3 Incidence of rib and vertebral fractures (as noted on CT imaging) that occur within 12 months of irradiation and are within the within 50% isodose line.

5.2.4 The urine concentration of an osteoclast-specific biomarker, urinary N-telopeptide (U-NTX) indicating osteoclastic activity will be assessed prior to SBRT and at each routine follow up visit (at 3 months, 6 months, 9 months, and 12 months post SBRT).

## 5.3 Exploratory Outcomes

5.3.1 We will contour the neurovascular bundle that runs in the intercostal space for each patient within at least 3 cm of the planning tumor volume. We will then utilize stored treatment planning information and the raystation planning system to calculate the dose that this nerve bundle received at the time of treatment. As patients have already been assessed for development of chest wall pain at each follow up, we will assess for a dose response relationship between the dose to the nerve bundle and the subsequent development of and grade of any chest wall pain per the CTCAE v5.

5.3.2 Urine concentrations (pg/mL) of markers of bone turnover activity such as P1NP (procollagen type 1 pro-peptide), sclerostin, OPG (osteoprotegerin), TRAP5B, and pentosidine (an advanced glycation end-product (AGE)); will be analyzed using ELISAs. These markers will be assessed prior to SBRT and at the 6 month follow up visit post SBRT).

5.3.3 Urine concentrations (pg/mL) of pain-associated cytokines derived from the Isoplexis Codeplex Secretome Human Adaptive Immune and Innate Immune Chips which include GM-CSF, IL-1β, IL-7,IL-17A, TNF-α, PDGF-BB, and VEGF will be assessed prior to SBRT and at the 6 month follow up visit post SBRT. In addition, other pro-inflammatory cytokines may be measured and analyzed on these chips as available. Also, if funding permits, the urine concentration (pg/mL) of pain-related neurotrophic growth factors (proNGF, proBDNF, GDNF) and neuropeptides (CGRP and Substance P) will be measured by ELISA.

# 6.0 Treatment Plan

## 6.1 Treatment Administration

Treatment will be administered on an outpatient basis.
Reported adverse events and potential risks of SBRT and risedronate are described in Section 8.

| **REGIMEN DESCRIPTION** | | | |
|---|---|---|---|
| **Agent** | **Dose** | **Route** | **Schedule** |
| Risedronate | 150 mg | Oral | Given once 7 – 21 days prior to initiation of SBRT |
| Matching Placebo | N/A | Oral | Given once 7 – 21 days prior to initiation of SBRT |

Standard of care radiation therapy with SBRT will be given over the course of 3 – 10 fractions to a total dose of 50 – 60 Gy at the discretion of the treating radiation oncologist. Specific dose fractionations between 3 – 10 fractions and constraints will be at the discretion of the treating radiation oncologist and may be prescribed every day or every other day. Respecting the following constraints are encouraged but meeting these constraints is not required for inclusion in the study. In many cases meeting the rib constraint will not be possible.

Treatment planning will be performed utilizing a vac lock or body fix bag and optional abdominal compression at the discretion of the treating radiation oncologist. Planning CT chest may be performed with or without contrast at the discretion of the treating radiation oncologist. Utilization of motion management with 4D cinematic CT or a slow scan is required for determination of the internal target volume (ITV). Clinical treatment volume (CTV) creation is not necessary and is not our standard treatment paradigm with SBRT for peripheral lung tumors. The planning target volume (PTV) is generally created as a 0.5 cm expansion from the ITV, however the exact dimensions of this expansion are at the discretion of the treating radiation oncologist.

## The following are encouraged but not required dose constraints.

### Three Fractions

| **Serial Tissue** | **Volume** | **Volume Max (Gy)** | **Max Point Dose (Gy)** | **Endpoint (≥Grade 3)** |
|---|---|---|---|---|
| Spinal Cord | <0.5 cc | 18 Gy (6 Gy/fx) | 22 Gy (7.33 Gy/fx) | myelitis |
| Cauda Equina | <5 cc | 21.9 Gy (7.3 Gy/fx) | 24 Gy (8 Gy/fx) | neuritis |
| Sacral Plexus | <3 cc | 22.5 Gy (7.5 Gy/fx) | 24 Gy (8 Gy/fx) | neuropathy |
| Esophagus* | <5 cc | 21 Gy (7 Gy/fx) | 27 Gy (9 Gy/fx) | stenosis/fistula |
| Ipsilateral Brachial Plexus | <3 cc | 22.5 Gy (7.5 Gy/fx) | 24 Gy (8 Gy/fx) | neuropathy |
| Heart/Pericardium | <15 cc | 24 Gy (8 Gy/fx) | 30 Gy (10 Gy/fx) | pericarditis |
| Great vessels | <10 cc | 39 Gy (13 Gy/fx) | 45 Gy (15 Gy/fx) | aneurysm |
| Trachea and Ipsilateral Bronchus* | <4 cc | 15 Gy (5 Gy/fx) | 30 Gy (10 Gy/fx) | stenosis/fistula |
| Skin | <10 cc | 22.5 Gy (7.5 Gy/fx) | 24 Gy (8 Gy/fx) | ulceration |
| Stomach | <10 cc | 21 Gy (7 Gy/fx) | 24 Gy (8 Gy/fx) | ulceration/fistula |
| Duodenum* | <5 cc | 15 Gy (5 Gy/fx) | 24 Gy (8 Gy/fx) | ulceration |
| Jejunum/Ileum* | <5 cc | 16.2 Gy (5.4 Gy/fx) | 27 Gy (9 cGy/fx) | enteritis/obstruction |
| Colon* | <20cc | 20.4 Gy (6.8 Gy/fx) | 30 Gy (10 Gy/fx) | colitis/fistula |
| Rectum* | <20cc | 20.4 Gy (6.8 Gy/fx) | 30 Gy (10 Gy/fx) | proctitis/fistula |
| Bladder wall | <20 cc | 15 Gy (5 Gy/fx) | 30 Gy (10 Gy/fx) | cystitis/fistula |
| Femoral Heads | <10 cc | 21.9 Gy (7.3 Gy/fx) | | necrosis |
| Renal hilum | <2/3 volume | 18.6 Gy (6.2 Gy/fx) | | malignant hypertension |

### Five Fractions

| Serial Tissue | Volume | Volume Max (Gy) | Max Point Dose (Gy) | Endpoint (≥Grade 3) |
|---|---|---|---|---|
| Spinal Cord | <0.5 cc | 22.5 Gy (4.5 Gy/fx) | 30 Gy (6 Gy/fx) | myelitis |
| Cauda Equina | <5 cc | 30 Gy (6 Gy/fx) | 34 Gy (6.4 Gy/fx) | neuritis |
| Sacral Plexus | <3 cc | 30 Gy (6 Gy/fx) | 32 Gy (6.4 Gy/fx) | neuropathy |
| Esophagus* | <5 cc | 27.5 Gy (5.5 Gy/fx) | 35 Gy (7 Gy/fx) | stenosis/fistula |
| Ipsilateral Brachial Plexus | <3 cc | 30 Gy (6 Gy/fx) | 32 Gy (6.4 Gy/fx) | neuropathy |
| Heart/Pericardium | <15 cc | 32 Gy (6.4 Gy/fx) | 38 Gy (7.6 Gy/fx) | pericarditis |
| Great vessels | <10 cc | 47 Gy (9.4 Gy/fx) | 53 Gy (10.6 Gy/fx) | aneurysm |
| Trachea and Ipsilateral Bronchus* | <4 cc | 18 Gy (3.6 Gy/fx) | 38 Gy (7.6 Gy/fx) | stenosis/fistula |
| Skin | <10 cc | 30 Gy (6 Gy/fx) | 32 Gy (6.4 Gy/fx) | ulceration |
| Stomach | <10 cc | 28 Gy (5.6 Gy/fx) | 32 Gy (6.4 Gy/fx) | ulceration/fistula |
| Duodenum* | <5 cc | 18 Gy (3.6 Gy/fx) | 32 Gy (6.4 Gy/fx) | ulceration |
| Jejunum/Ileum* | <5 cc | 19.5 Gy (3.9 Gy/fx) | 35 Gy (7 Gy/fx) | enteritis/obstruction |
| Colon* | <20cc | 25 Gy (5 Gy/fx) | 38 Gy (7.6 Gy/fx) | colitis/fistula |
| Rectum* | <20cc | 25 Gy (5 Gy/fx) | 38 Gy (7.6 Gy/fx) | proctitis/fistula |
| Bladder wall | <20 cc | 18.3 Gy (3.65Gy/fx) | 38 Gy (7.6 Gy/fx) | cystitis/fistula |
| Femoral Heads | <10 cc | 30 Gy (6 Gy/fx) | | necrosis |
| Renal hilum | <2/3 volume | 23 Gy (4.6 Gy/fx) | | malignant hypertension |

**Ten Fractions**

| Serial Tissue | Volume | Volume Max (Gy) | Max Point Dose (Gy) | Endpoint (≥Grade 3) |
|---|---|---|---|---|
| Spinal Cord | <0.5 cc | 32 Gy (3.2 Gy/fx) | 36 Gy (3.6 Gy/fx) | myelitis |
| Cauda Equina | <5 cc | 36 Gy (3.6 Gy/fx) | 40 Gy (4.0 Gy/fx) | neuritis |
| Sacral Plexus | <3 cc | 37 Gy (3.7 Gy/fx) | 44 Gy (4.4 Gy/fx) | neuropathy |
| Esophagus* | <5 cc | 40 Gy (4 Gy/fx) | 50 Gy (5.0 Gy/fx) | stenosis/fistula |
| Ipsilateral Brachial Plexus | <3 cc | 37 Gy (3.7 Gy/fx) | 44 Gy (4.4 Gy/fx) | neuropathy |
| Heart/Pericardium | <15 cc | 39 Gy (3.9 Gy/fx) | 45 Gy (4.5 Gy/fx) | pericarditis |
| Great vessels | <10 cc | 58 Gy (5.8 Gy/fx) | 64 Gy (6.4 Gy/fx) | aneurysm |
| Trachea and Ipsilateral Bronchus* | <4 cc | 32 Gy (3.2 Gy/fx) | 50 Gy (5.0 Gy/fx) | stenosis/fistula |
| Skin | <10 cc | 38 Gy (3.8 Gy/fx) | 45 Gy (4.5 Gy/fx) | ulceration |
| Stomach | <10 cc | 35 Gy (3.5Gy/fx) | 45 Gy (4.5 Gy/fx) | ulceration/fistula |
| Duodenum* | <5 cc | 32 Gy (3.2 Gy/fx) | 45 Gy (4.5 Gy/fx) | ulceration |
| Jejunum/Ileum* | <5 cc | 32 Gy (3.2 Gy/fx) | 45 Gy (4.5 Gy/fx) | enteritis/obstruction |
| Colon* | <20cc | 36 Gy (3.6 Gy/fx) | 50 Gy (5.0 Gy/fx) | colitis/fistula |
| Rectum* | <20cc | 38 Gy (3.8 Gy/fx) | 52 Gy (5.2 Gy/fx) | proctitis/fistula |
| Bladder wall | <20 cc | 32 Gy (3.2 Gy/fx) | 54 Gy (5.4 Gy/fx) | cystitis/fistula |
| Femoral Heads | <10 cc | 38 Gy (3.8 Gy/fx) | | necrosis |
| Renal hilum | <2/3 volume | 35 Gy (3.5 Gy/fx) | | malignant hypertension |

## 6.2 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed for chest wall pain, however use of these medications must be noted. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

## 6.3 Duration of Therapy

The hypothesized bone structural benefit of bisphosphonates with radiation is due to inhibition of early osteoclast activation within as little as 1 week of SBRT. In our preclinical studies, risedronate was only

given just prior to irradiation, and it was not given at all after irradiation was completed. Osteoclast activation only lasted for 1 week post irradiation in rodent models. In non-human primate models, the first follow up scans were performed at 2 months post irradiation, and these scans indicated maximal bone loss had already occurred which was persistent but not worsening on subsequent scans. For this reason, risedronate will be given only once prior to SBRT, at a dose of 150 mg, which is the recommended monthly dose in the setting of osteoporosis in post-menopausal females.

SBRT is given over the course of 3 to 10 treatments and generally this is performed over the course of 1.5 - 2 weeks. Radiation treatments are given every day or every other day Monday through Friday with the exclusion of the weekends or major holidays. In the absence of treatment delays due to adverse events, radiation treatments may continue until the planned treatment dose is reached or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study

General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

## 6.4 Duration of Follow-up

Follow-up for serious adverse events and mortality after the single dose of 150 mg of risedronate or placebo is administered will take place during the routine clinic visits during radiation treatment. Radiation treatments will occur within 1 – 3 weeks of taking the study drug. The 30 day follow-up window that is part of mandatory DSMC-SAE reporting will be considered 30 days from the end of all treatments of radiation. This visit can be either a phone call or a visit in person to review adverse events and may be conducted and documented in the medical record by either research study staff RNs or the treating physician. A window of +/- 7 business days is allowed for the 30 day followup assessment.

Specific toxicity related to radiation pneumonitis, radiation fibrosis, and chest wall pain will be collected at each followup point as per appendices K – M.

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will be followed for a minimum of 3 months for assessment of the primary objective.

Patients will be ideally followed in total for 12 months after completion of radiation therapy for the purposes of this study.

In the event that patients develop progressive disease or a new cancer, requiring additional chemotherapy they will be withdrawn from further study directed followup. In these situations, the followup schedules and imaging become dramatically different from what is directed on this protocol. Additionally further systemic chemotherapy treatments can heavily alter bone density/cortical thickness. As such, if patients develop new disease requiring additional systemic chemotherapy treatment outside of their initial SBRT, they will be withdrawn from study for further follow ups/study directed imaging. Any data that was collected prior to study withdrawal will still be used in analysis. **Immunotherapy or**

**hormonal therapy for breast or prostate cancer will not be considered reasons for withdrawal**. Cryoablation or radiofrequency ablation will not be considered a reason for withdrawal from study.

## 6.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in section 3.2 or 6.4 applies. As above if patient develop progressive or new disease requiring additional systemic chemotherapy, they will be removed from study for further protocol directed assessments.

## 6.6 Study Calendar

| | Baseline Prior to SBRT | Dosing (7-21 days before SBRT) | During SBRT | 1 month Post SBRT | 3[f] months post SBRT | 6[f] months Post SBRT | 9[f] months Post SBRT | 12[f] months Post SBRT |
|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | |
| Demographics<br>Medical history<br>History of diabetes<br>Physical exam<br>Performance status<br>Vital signs<br>Height, Weight, $M^2$ | X | | | | | | | |
| Current Medications list | X | | | | X | | | |
| Current or prior use of rank ligand inhibitors, bisphosphonates, and steroids with dates of use and dose as per Appendix G.[h.] | X | | | | X | X | X | X |
| CT chest with or without contrast | X[a] | | | | X | X | X | X |
| Risedronate or placebo | | X[c] | | | | | | |
| Urine sample[d] | X | | | | X | X | X | X |
| Serum Calcium<br>EGFR<br>Serum Creatinine<br>Pregnancy test[b] | X | | | | | | | |
| Adverse event evaluation (Appendix E) | | | | | X | | | |
| Specific Radiation Related Chest wall Toxicity (Appendix K) | | | | X[e] | X | X | X | X |
| Follow up phone call for assessment of adverse events without imaging (Appendix F) | | | | X | | | | |
| Fracture Incidence (Appendix Q) | X | | | | X | X | X | X |
| Radiation Treatment Details (Appendix N) | | | X[g] | | | | | |

[a] Pre-SBRT CT chest scan will be the treatment planning scan. Fracture incidence will be assessed on CT scans

[b] Urine pregnancy test (women of childbearing potential) performed within 1 week of treatment planning simulation for radiation.

[c.] Given once at 7 – 21 days prior to initiation of SBRT

[d]. For urine sample pick-up and transport, call Jeff Willey at 864-506-0672 (mobile), 336-713-7637 (office). If not available, call Alex Borg at 973-865-4279 (mobile).

e. At the 30-Day time point this can be collected over the phone

f. Every 3 month follow-up, and CT imaging will have a window of +/- 8 wks

g. Appendix N may be completed during SBRT but should be completed within 12 weeks of completing SBRT

All pre-study activities must be completed within 12 weeks of the start of study drug including labs

# 7.0 Measurement of Effect

## 7.1 Cortical Thickness Mapping Approach and Radiation Dose Mapping

We will utilize our published novel method of cortical thickness mapping as outlined below. Ribcage and vertebral cortical thickness mapping will be performed for each patient utilizing the CT scan at time of "simulation" or treatment planning/mapping and routine standard of care follow-up imaging at 3 months, 6 months, 9 months, and 12 months, which would be performed regardless of inclusion on this study.

The bony anatomy of the thorax will be segmented for each CT scan using automated thresholding techniques and manual editing in Mimics (v16.0 Materialise, Leuven, Belgium) for Windows. Individual contours of the entire ribs and vertebral bodies from cervical (C) level C7 through thoracic (T) level T12 will be constructed in treatment planning software.

These contours will be utilized to construct 3D surfaces containing over 100,000 vertices throughout the bony thorax using Stradwin software (v5.0 Cambridge University, Cambridge, England) for Windows.

Our unique cortical bone mapping algorithm relies on a global cortical density measurement, which is factored into a piecewise defined Heaviside step function derived from the convolution of the in-plane and out-of-plane point spread functions (PSFs) of each CT scan.

The global cortical bone density for each CT scan will be determined by collecting density measurements at each vertex. The CT values along a 12 mm line normal to the cortical surface at each of the approximately 50,000 vertices of the 3D rib surfaces will be obtained and applied to the validated Ct.Th estimation model constrained by the cortical density and out-of-plane blur. Cortical thickness maps will be constructed using the pre-SBRT planning CT scan and 3 month post-SBRT follow up CT scan for each treated patient for evaluation of the primary objective. We will similarly perform this analysis at the 6 months, 9 months, and 12 months post SBRT time points for evaluation of secondary objectives.

The received radiation doses to the surface of the ribcage at each vertex will be obtained in MIM and then registered to the corresponding Ct.Th map using iterative closest point (ICP) registration in MATLAB (v2014a, MathWorks, Natick, MA). Each rib will be subdivided into evenly spaced cylindrical subsections (30 subsections per rib) along its centerline using a custom MATLAB algorithm.

Rib vertices from the pre-SBRT CT scans will be spatially aligned with the post-SBRT CT in 3D Slicer (v 3.6, http://www.slicer.org) in Windows to define homologous rib subsections on the post-SBRT CT scan. A rigid transform consisting of translation and rotation operations will be computed and applied to align the pre- and post- treatment ribcage surfaces. A series of approximately twenty-five points will be manually selected on the ribcage surface to derive each transform. An affine transform will then be computed using an iterative closest point (ICP) algorithm and applied to the transformed ribcage surface to account for geometric interscan variation. The mean dose and Ct.Th for each homologous rib region will be calculated from the Ct.Th and dose measurements at all vertices within that region.

Bone within the treatment field (within the 50% isodose line) will be segmented into homologous regions receiving dose at 10 Gy intervals, of 0-10 Gy, > 10 – 20Gy, >20 – 30 Gy, > 30 – 40 Gy, and >40 Gy, and in each region the mean cortical thickness will be calculated. The % change in cortical thickness will be compared in each region between patients who received risedronate and those who received placebo.

## 7.2 Incidence and Grade of Chest Wall Pain

Patients will be assessed at each routine follow up for development and or resolution of any chest wall pain/discomfort within the 50% isodose line. This will be graded per modified CTCAE v.5.

## 7.3 Detection of Rib/Vertebral Body fractures

The incidence of rib and or vertebral fractures within the radiation treatment field within the 50% isodose line will be collected from standard follow-up CT imaging at 3, 6, 9, and 12 months post SBRT.

## 7.4 Urine Biomarkers of Osteoclastic Activity and Bone Turnover

A single urine sample will be collected at baseline and at each follow up point (3,6,9,12 months). Samples will be collected in clinic and immediately transported to the laboratory of Dr. Jeffrey Willey on campus for storage in an minus 80 degrees C freezer designed for lab specimen storage. Urinary N-telopeptide (U-NTX) will be measured using ELISA based on an immobilized synthetic peptide with a specific sequence of amino acids matching a section of the N telopeptide (NTX) of type 1 collagen. Samples will be destroyed in biohazard waste immediately after analysis is complete.

The following detailed information on collection and analysis is provided from pacific biomarkers https://pacbio.com/biomarker/assay-detail/148/

Specimen Type: Urine (2nd morning void preferred; do not add preservative)

Optimum Volume: 1 mL

Stability:

| 2-8°C | -20°C | -70°C |
|---|---|---|
| 1 week | 3 months | 1 year |

Reporting units: nM BCE/mmol Cr (normalized)

Method: ELISA

Biological or Clinical Significance:

Bone resorption is a function of osteoclasts. These cells remove the mineral from bone and break down the organic matrix that is primarily comprised of type I collagen. Collagen is a cross-linked fibrous protein that forms the fabric of bone and most other connective tissues. Bone contains three polypeptide chains wound together in a helical structure. The ends of these chains (known as telopeptides) provide the intermolecular cross-linking that gives collagen its strength and resiliency. As these cross-linked domains from bone and other skeletal connective tissues are broken down, the pyridinoline cross-linking domains are released and ultimately excreted into the urine in the form of small peptides bound to pyridinoline (70%) and free pyridinoline (30%). One type of peptide-bound pyridinoline is the cross-linked N-telopeptide (NTX) which is unique to type I bone collagen. NTX can be used to identify fast losers of bone, to monitor therapy, to measure dose response, or to determine patient compliance with therapeutic prescription(s).

A growing body of clinical studies has shown that urinary NTx provides a sensitive marker of human bone resorption. Its specificity is based on originating solely from type I collagen, being particularly enriched as a cross-linking structure in bone type I collagen and being produced directly as a proteolytic neoepitope by osteoclast activity during bone resorption. Analysis of urine specimens has certain advantages, including ease of collection and reduced biohazard precautions for clinical laboratory personnel than with bloodbased specimens. However, the obtained results need to be normalized to creatinine.

Principle of Test Method:

The NTX assay is a competitive, enzyme-linked immunosorbent assay (ELISA) for the quantitative measurement of the NTX in human urine. NTX is reported as a normalized ratio to urinary creatinine in order to account for variations in urine flow rate. Therefore NTX and urine creatinine are preferably tested from the same aliquot.

### 7.5 Evaluable for toxicity:

All patients will be evaluable for toxicity from the time of their first treatment with risedronate, which will be given prior to start of SBRT

## 8.0 Adverse Events List and Reporting Requirements

### 8.1 Adverse Event List for Stereotactic Body Radiotherapy (SBRT)

**Likely risk and side effects**

- Fatigue
- Redness of irritation of the skin in the treatment area
- Hair loss in the treatment area
- For tumors near the esophagus, irritation of the esophagus and sore throat/difficulty swallowing
- Some soreness of the ribs with an increased risk of rib fracture
    - Treatment for such symptoms usually consists of rest, heat, and pain medication.
- Damage to surrounding normal lung and/or collapse of a portion of treated lung
- Changes in the lungs as the tumor shrinks
    - This includes expected "scarring".
    - In most patients, no noticeable symptoms will result from this lung damage.

**Less likely risk and side effects**

- Cough
- Difficulty breathing
    - Decrease in lung function parameters
    - Which may result in temporary or permanent need for supplemental oxygen
- Increased phlegm production
- Fever
- Severe pain or skin damage leading to an open wound
- Damage to the stomach or bowel
    - This can lead to ulceration or perforation with a risk of infection and death.
- Damage to the spinal cord
    - can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs

- Damage to the large blood vessels surrounding the heart
  - This could cause coughing up of blood and possibly death
- Damage to the heart muscle, which can cause heart attack, heart failure, or death
- Damage to the lining of the heart, which can cause fluid accumulation around the heart
  - This may cause chest pain, shortness of breath, and/or irregular or rapid heart beat
- Tumors near vertebrae there is increased risk of vertebral compression fracture
  - If vertebral fracture is already present, there is risk of progression of fracture.
- With any radiation therapy, there may be a very small chance that the radiation could cause a secondary cancer. The excess cancer risk from the radiation is estimated to be about 3.416% with at least 7 years between the receipt of radiation and the second cancer forming. The lifetime cancer risk is about 20% assuming several decades of follow-up.
- No additional scans outside of standard of care will be taken for this study.

## 8.2 Adverse Event List for Risedronate

**Likely risk and side effects**

- Bone and joint pain
- Abdominal discomfort/indigestion

**Uncommon/Rare risk and side effects**

- Eye pain, redness, swelling, sensitivity to light and or decreased vision
- Glossitis
- Jaw osteonecrosis with pain in the mouth or teeth
- Numbness or feeling of heaviness in the jaw
- Poor healing of gums
- Loose teeth

**Very rare**

- Allergic and skin reactions
  - Hives, rash with or without blisters
  - Facial/tongue/lip swelling, trouble swallowing or breathing
- Symptoms of low blood calcium (Numbness, tingling, muscle spasms)

## 8.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).
- A modified CTCAE 5 chest wall pain grading scale accounting for control with NSAID vs Narcotic, gabapentin, or nerve block use is included in Appendix K
- We have no mechanistic reason to suspect that concurrent use of risedronate with radiation will increase pulmonary toxicities and these medications are not contraindicated during SBRT. Preliminary review of our own small retrospective database of patients concurrently receiving SBRT while on bone anti-resorptive therapies has not yielded any excess or un-expected toxicity. However, as there is only limited retrospective data in this setting, we will plan to assess for excess pulmonary toxicities once 50% of patients have been recruited and reached the 3 month followup point. If there is > 30% grade 3 or higher pneumonitis, we will discontinue the study.

- **Expectedness**:
  - AEs can be 'Unexpected' or 'Expected'
  - (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:
  Definite – The AE **is clearly related** to the study treatment.
  Probable – The AE **is likely related** to the study treatment.
  Possible – The AE **may be related** to the study treatment.
  Unlikely – The AE **is doubtfully related** to the study treatment.
  Unrelated – The AE **is clearly NOT related** to the study treatment.

## 8.4 DSMC SAE Reporting Requirements

The Data and Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

## 8.5 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

## 8.6 Sponsor Reporting Requirements

This study has full support of the Thoracic multidisciplinary committee and has been presented for the Disease Oriented Team (DOT) for review with core senior faculty. Additionally, we have full support of the departments of medical oncology and radiation oncology. We will be applying for R grant funding, as well as funding through the NCORP and radiation oncology institute.

# 9.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.2. We are in the process of submitting this protocol for IND exemption through the FDA and have completed the necessary paperwork for this.

## 9.1 Pharmaceutical Accountability

Risedronate (Actonel) is commercially available.

## 9.2 Product Information for ACTONEL® (risedronate sodium) tablets

**Product description:** Risedronate is a pyridinyl bisphosphonate. The chemical name is [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt. It has an affinity for bone hydroxyapatite and inhibits osteoclast mediated bone resorption.

**Solution preparation:**
Risedronate sodium is a fine, white to off-white, odorless, crystalline powder. It is soluble in water and in aqueous solutions, and essentially insoluble in common organic solvents. It is given orally in tablet form.

**Dosage forms and ingredients:**
**The following information below was obtained from the product monograph from Allegran Pharma Co. Markham, Ontario L6G0B5 August 2017, Submission Control 205107**

**ACTONEL®**
Medicinal Ingredients: Each risedronate sodium tablet for oral administration contains the equivalent of 5, 30, 35, or 150 mg of anhydrous risedronate sodium in the form of the hemipentahydrate with small amounts of monohydrate. Nonmedicinal Ingredients (Film-coated Tablets): Crospovidone, ferric oxide red (35 mg), ferric oxide yellow (5 and 35 mg), hydroxypropyl cellulose, hypromellose, indigo carmine (150 mg), lactose monohydrate (5, 30 and 35 mg), magnesium stearate, microcrystalline cellulose, polyethylene glycol, colloidal silicon dioxide and titanium dioxide.

| Dosage Strength | Description | Packaging |
|---|---|---|
| 5 mg | film-coated, oval-shaped, yellow tablets with "RSN" engraved on one face and "5 mg" engraved on the other | carton of 28 blister packaged tablets |
| 30 mg | film-coated, oval-shaped, white tablets with "RSN" engraved on one face and "30 mg" engraved on the other | bottle of 30 tablets |
| 35 mg | film-coated, oval-shaped, orange tablets with "RSN" engraved on one face and "35 mg" engraved on the other | carton of 4 blister packaged tablets |
| 150 mg | film-coated, oval-shaped, blue tablets with "RSN" engraved on one face and "150 mg" engraved on the other | carton of 1 blister packaged tablet |

**Storage requirements and Stability:**
All dosages are recommended for storage and are stable at controlled room temperature 20° to 25°C (68° to 77°F)

**Route of administration:**

| Route of Administration | Dosage Form/ Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| oral | ACTONEL film-coated tablet 5 mg, 30 mg, 35 mg, and 150 mg | lactose monohydrate (5 mg, 30 mg and 35 mg) |

**Disposal:**
There are no specific disposal recommendations for Actonel.

### 9.3 Creation of Risedronate Placebo
The Wake Forest Investigational Drug Service (IDS) Pharmacy staff under leadership of Brian Strittmatter PharmD, MS is currently involved with an unrelated research protocol that also utilizes 150 mg of risedronate vs placebo. Therefore, we already have the necessary infrastructure in place for creation of a look-alike placebo and randomization.

## 10.0 Data Management

| Data Collection Form | Data Storage Location |
|---|---|
| Informed consent document | EPIC |
| Protocol registration form | WISER/OnCore |
| All CT scans imaging and reports | EPIC/PACS |
| Adverse event log Appendix E | Oncore |
| Current Medications (Appendix G) | Oncore |
| Medication/Placebo administration form (Appendix H) | Oncore |
| Specific radiation related toxicities<br>Modified CTCAE Chest wall pain<br>Radiation pneumonitis<br>Radiation Fibrosis<br>(Appendix K and the pre-filled AE log) | OnCore |
| Radiation Treatment Details (Appendix N) | OnCore |
| Cortical Thickness Change (Appendix O) | OnCore |
| Urine bone turn over data (Appendix P) | OnCore |
| Fracture Incidence (Appendix Q) | OnCore |
| Adverse Events Log | WISER/OnCore |
| Biomarkers of Bone Turnover Activity | REDCap |
| Pain-Associated Cytokines | REDCap |

### Double Blind Design

We will work cooperatively with our IDS pharmacy supplying each patient either a single tablet of risedronate 150 mg or a single tablet of placebo. We will work directly with IDS pharmacy staff 336-716-3258, to procure identical placebo tablets as well as procedures for un-blinding and drug masking. As the hospital already has an unrelated protocol utilizing 150 mg risedronate vs placebo, many of these procedures are already in place. Patients will enroll though CDPM and be randomized through OnCore, but the investigator will not have knowledge of the randomization arm to which any patient has been assigned. The dispensing pharmacy will provide blinded samples and only the pharmacy will hold keys to un-blinding. At the conclusion of the study, when all patients have completed 12 months of follow up, the investigators will be unblinded to randomization of each patient.

# 11.0 Statistical Considerations

## 11.1 Analysis of Primary Objective

The percent change in mean cortical thickness within regions receiving 30 Gy or more will be calculated from time of the treatment planning CT scan to 3 months post SBRT. This % change will be compared between the patients receiving risedronate and those receiving placebo.

## 11.2 Analysis of Secondary Objectives

### 11.2.1 Percent change in cortical thickness across all time points

The percent change in mean cortical thicknesses from baseline will be assessed at 3 months, 6 months, 9 months, and 12 months post SBRT separately within regions of bone receiving 0 – 10 Gy, >10 – 20 Gy, > 30 – 40 Gy, and >40Gy. These outcomes will be compared using repeated measures analysis of variance (ANOVA).

### 11.2.2 Incidence and grade of chest wall pain

The incidence and grade of chest wall pain occurring inside the 50% isodose line will be collected and reported per modified CTCAE v5.0 (Appendix K) at 3 months, 6 months, 9 months, and 12 months post SBRT for all patients. Results will be compared between patients receiving placebo or risedronate. The incidence of G3 or greater chest wall pain will also be correlated with the volume of chest wall receiving at least 30 Gy or greater. The chest wall contour is defined as a 2 cm expansion from lung, from the costovertebral angle to the sternum.

### 11.2.3 Incidence of rib or vertebral fractures

The incidence of rib or vertebral fractures within the treatment field occurring at any time during the entire course of the study (12 months), will be reported and compared between patients receiving placebo or risedronate.

#### 11.2.4 Urinary excretion of N-telopeptide (NTX)

The concentration of urinary NTX will be assessed at each time point from baseline to the conclusion of the study at 12 months. Results will be directly compared in each group.

## 11.3 Analysis of Exploratory Objectives

#### 11.3.1 Rib neurovascular bundles

We will evaluate the correlation between calculated doses to specific substructures in the chest wall and patient-reported pain, stratified by treatment group.

#### 11.3.2 Urinary markers of bone turnover

We will conduct repeated measures analyses on urinary markers of bone turnover activity (one model per marker) and assess whether there is evidence of meaningful group by time interaction in the markers.

#### 11.3.3 Urinary markers of pain-associated cytokines

Similar to above, we will conduct repeated measures analyses on urinary makers of pain-related biomarkers (cytokines and growth factors) where again we will be focused on examining evidence of group by time interaction.

## 11.4 Power and Sample Size

Per analysis of our retrospective human data and preclinical data, we estimate that the mean cortical thickness for both cases and controls pre SBRT will be approximately 1.35 mm. At 3 months, in the absence of any treatment, we estimate approximately 16.7% loss of cortical thickness to bones to 1.13 mm (thus resulting in a mean change of 0.22 mm in controls) within the treatment field in regions of bone receiving ≥ 30 Gy. Conservatively, if risedronate use limits loss of cortical thickness by at least half on a percentage scale (i.e., expected cortical thickness at 3 months in treatment group 8.4% lower, or 1.24 mm, corresponding to an expected mean change in treatment group of 0.11 mm), and assuming a standard deviation of delta cortical thickness in both treatment and control patients of 0.20,[4] then with a power of 0.80 and a one-tailed alpha of 0.05, we anticipate that we will need 42 patients per group to achieve desired power to illustrate significantly higher preservation of cortical thickness at 3 months post SBRT.

There is no human data to accurately estimate how significantly risedronate will limit bone loss following SBRT, however in our pre-clinical rodent models, cortical thickness was preserved in all mice receiving risedronate and in two mice cortical thickness increased. We have no mechanistic reason to suspect that risedronate would cause increased bone loss and therefore are utilizing a one-tailed alpha in our calculations.

## 11.5 Estimated Accrual Rate

On review of treatment planning records for the last 1 month in our department here at the main campus of Wake Forest Hospital, we have treated 18 patients who would have qualified for inclusion on this study. This is a reasonable representation of our average treatment population. Conservatively, we estimate accrual of 5 – 10 patients per month. Roughly 2/3 of our SBRT plans unavoidably exceed dosimetric constraints for the ribs/chest wall**.**

## 11.6 Estimated Study Length

2 - 3 years

## 11.7 Interim Analysis Plan

There is no interim analysis of primary or secondary objectives planned for this study.
Toxicity analysis:
We have no mechanistic reason to suspect that concurrent use of risedronate with radiation will increase pulmonary toxicities, and these medications are not contraindicated during SBRT. Preliminary review of our own small retrospective database of patients concurrently receiving SBRT while on bone anti-resorptive therapies has not yielded any excess or un-expected toxicity. However, as there is only limited retrospective data in this setting, we will plan to assess for excess pulmonary toxicities once 50% of patients have been recruited and reached the 3 month followup point. If there is > 30% grade 3 or higher pneumonitis, we will discontinue the study.

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***The following Appendices are required for all WFBCCC cancer treatment protocols.***

*Add additional appendices as needed.*

***ALL** data collection forms must be included as protocol appendices at the time the protocol is submitted to the WFBCCC Protocol Review Committee (PRC) for review.*

# Appendix A – Eligibility Checklist

| IRB Protocol No. | WFBCCC Protocol No. 99518 |
|---|---|

**Study Title:** CCCWFU # 99518

*A Randomized Clinical Trial of Prophylactic Risedronate for Patients with Peripheral Lung Tumors Treated with SBRT*

**Principal Investigator: Michael Farris MD**

| Inclusion Criteria (as outlined in study protocol) | Criteria is met | Criteria is NOT met | Source Used to Confirm * (Please document dates and lab results) |
|---|---|---|---|
| Patients must be 18 years or older, but there is no upper limit on age of inclusion. | ☐ | ☐ | |
| Patients must have a peripheral lung tumor that is amenable to SBRT as determined by the treating radiation oncologist. To be classified as a peripheral lung tumor, the tumor edge (the edge of the gross tumor volume or GTV in radiation treatment planning software) must be within 2 cm of the chest wall. This is determined by the treating radiation oncologist. The chest wall is defined as the chest wall musculature or ribs/vertebrae immediately adjacent to the lungs. | ☐ | ☐ | |
| Patients must have ECOG status of 0-3 | ☐ | ☐ | |
| Patients must have life expectancy of at least 3 months as determined by the treating radiation oncologist | ☐ | ☐ | |
| Patients must have the ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative) | ☐ | ☐ | |
| **Exclusion Criteria (as outlined in study protocol)** | **Criteria NOT present** | **Criteria is present** | **Source Used to Confirm * (Please document dates and lab results)** |
| Tumor edge is greater than 2 cm from the chest wall. The edge of tumor is the edge of the gross tumor volume or GTV as defined in radiation treatment planning software. This is determined by the treating radiation oncologist | ☐ | ☐ | |
| Tumors that are expected to require more than 10 fractions of radiation as determined by the treating radiation oncologist. | ☐ | ☐ | |
| History of using bone anti-resorptive agents including bisphosphonates or RANK-L inhibitors within the last 1 year. | ☐ | ☐ | |

| | | | |
|---|---|---|---|
| Inability to stand or sit upright for at least 30 minutes, which is necessary for ingestion of risedronate. | ☐ | ☐ | |
| Hypocalcemia defined as serum total calcium lower than 8.5 mg/dL on most recent bloodwork that is within 3 months of administration of study drug/placebo | ☐ | ☐ | |
| Severe renal impairment (EGFR <30 mL/min) on most recent bloodwork that is within 3 months of administration of study drug/placebo | ☐ | ☐ | |
| Known allergy to zoledronate or other bisphosphonates | ☐ | ☐ | |
| Surgery affecting the bone or dental operations within the last 6 months<br><br>Dental operations do not include routine cleaning or cavity fillings<br><br>Dental operations that exclude patients refer to any manipulation of mandible<br><br>*This will be explicitly asked and documented by treating radiation oncologist in the EMR | ☐ | ☐ | |
| Positive urine pregnancy test in women of child bearing potential within 1 week of registration. Pregnant women are excluded from this study because radiation has clear teratogenic and potentially abortifacient risks. | ☐ | ☐ | |

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”
**Principal Investigator signature can be obtained following registration if needed

# Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___$m^2$

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

*Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.*

*Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.*

# Appendix C – Race & Ethnicity Verification Form

*Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.*

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

---

***Internal use only:***

Name: _____ MRN#: _____

*Was the self-reported race and ethnicity of the participant verified at the time of consent?*
☐ **Yes** ☐ **No**

*Was a discrepancy found?* **Yes** ☐ **No** ☐
*If yes, please provide what is currently indicated in the EMR:*
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

# Appendix D – Mandatory DSMC SAE Reporting Guidelines

| | |
|---|---|
| **Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP** | **Date: 02/11/2021** |

**Mandatory DSMC SAE Reporting Requirements in WISER**

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites. There are three types of trials that are included in this category:
    a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
    c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients

enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

**THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.**

**What is considered during protocol intervention**?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

**What is considered as an Unexpected Grade 4 event?**

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

**DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:**

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

**Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):**

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***

13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

**The Clinical Members of DSMC to Notify by Phone or Page:**

| Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday |
|---|---|---|---|---|---|---|
| Lesser | Hughes | Goodman | Reed | Porosnicu | Seegars | Lesser |
| Hughes | Goodman | Reed | Porosnicu | Seegars | Lesser | Hughes |
| Goodman | Reed | Porosnicu | Seegars | Lesser | Hughes | Goodman |
| Reed | Porosnicu | Seegars | Lesser | Hughes | Goodman | Reed |
| Porosnicu | Seegars | Lesser | Hughes | Goodman | Reed | Porosnicu |
| Seegars | Lesser | Hughes | Goodman | Reed | Porosnicu | Seegars |

**Glenn Lesser, MD** – Hematology Oncology **Mercedes Porosnicu, MD**-- Hematology Oncology **Ryan Hughes, MD** – Radiation Oncology
**Michael Goodman, MD** -- Hematology Oncology
**Daniel Reed, MD** -- Hematology Oncology
**Mary Beth Seegars, MD** -- Hematology Oncology

**Definition of Unavailable:**

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the

table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

**DSMC CLINICAN RESPONSIBILITY:**

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment shouldbe considered.

**AMENDMENTS TO PREVIOUS REPORTS**

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

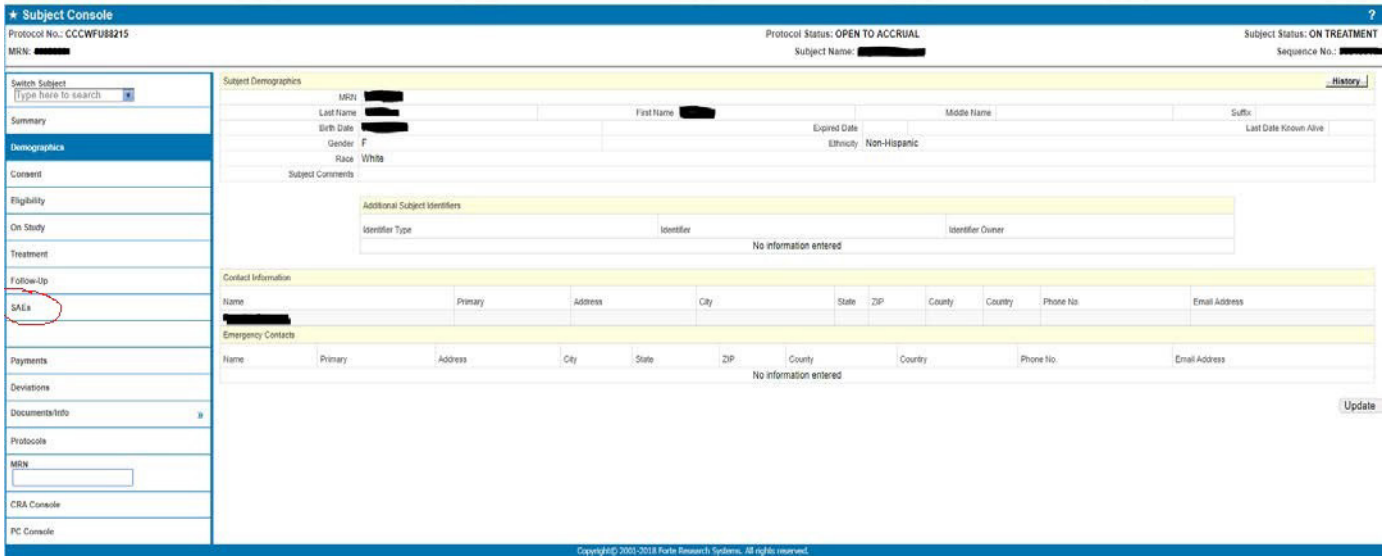
**Acronyms**

**AE** – Adverse Event
**DSMC**-Data and Safety Monitoring Committee
**SAE**-Serious Adverse Event
**WFBCCC** – Wake Forest Baptist Comprehensive Cancer Center
**NCI**-National Cancer Institute
**WISER –**Wake Integrated Solution for Enterprise Research

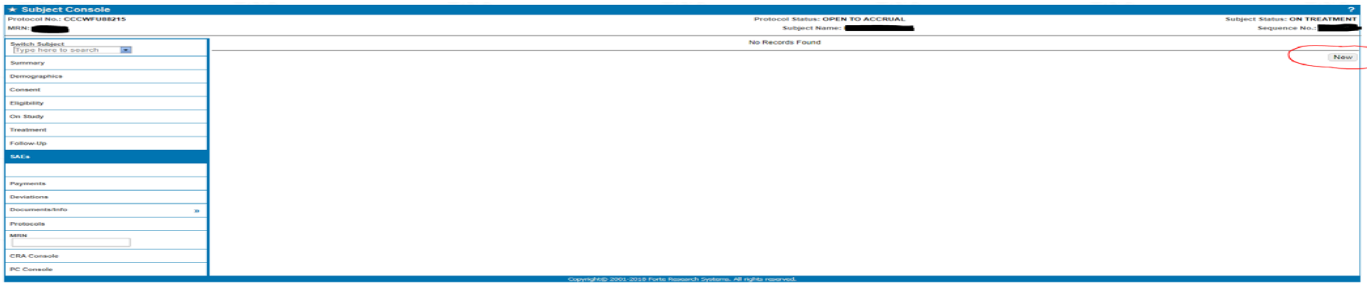
**Screen Shots:**

The following screen shots come from the SAE Console within the Subject Console in WISER.

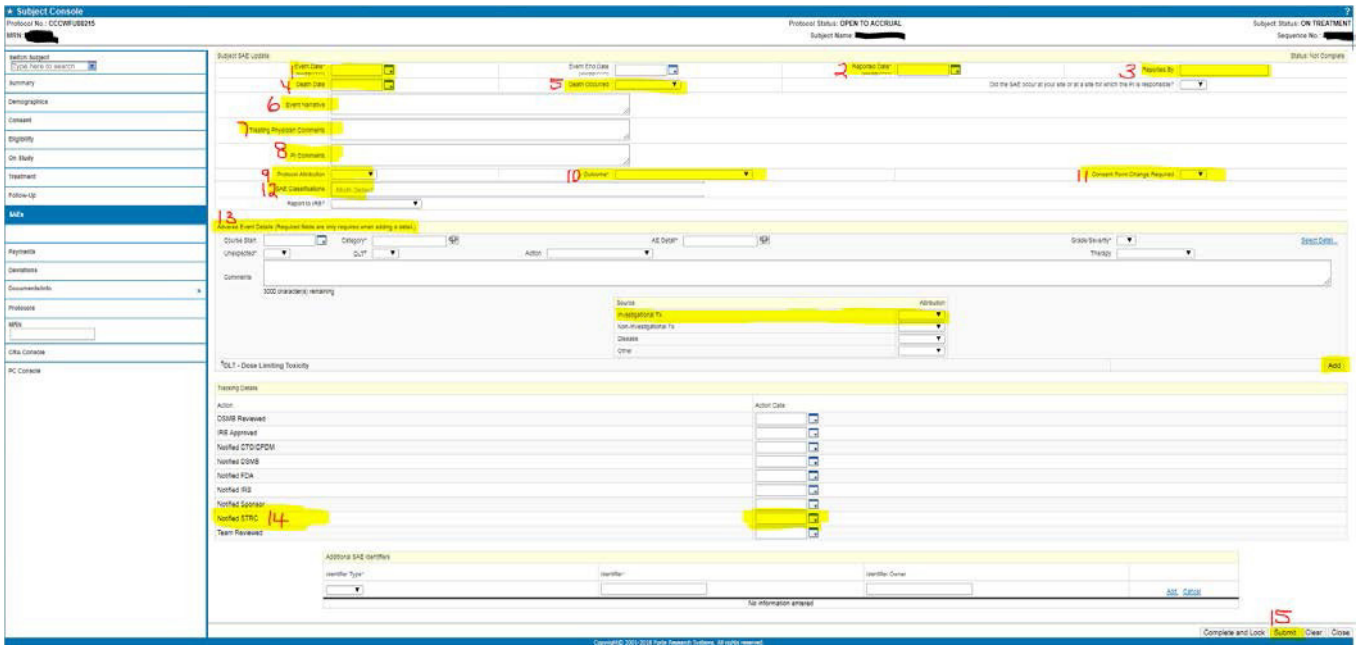
Screen Shot 1:



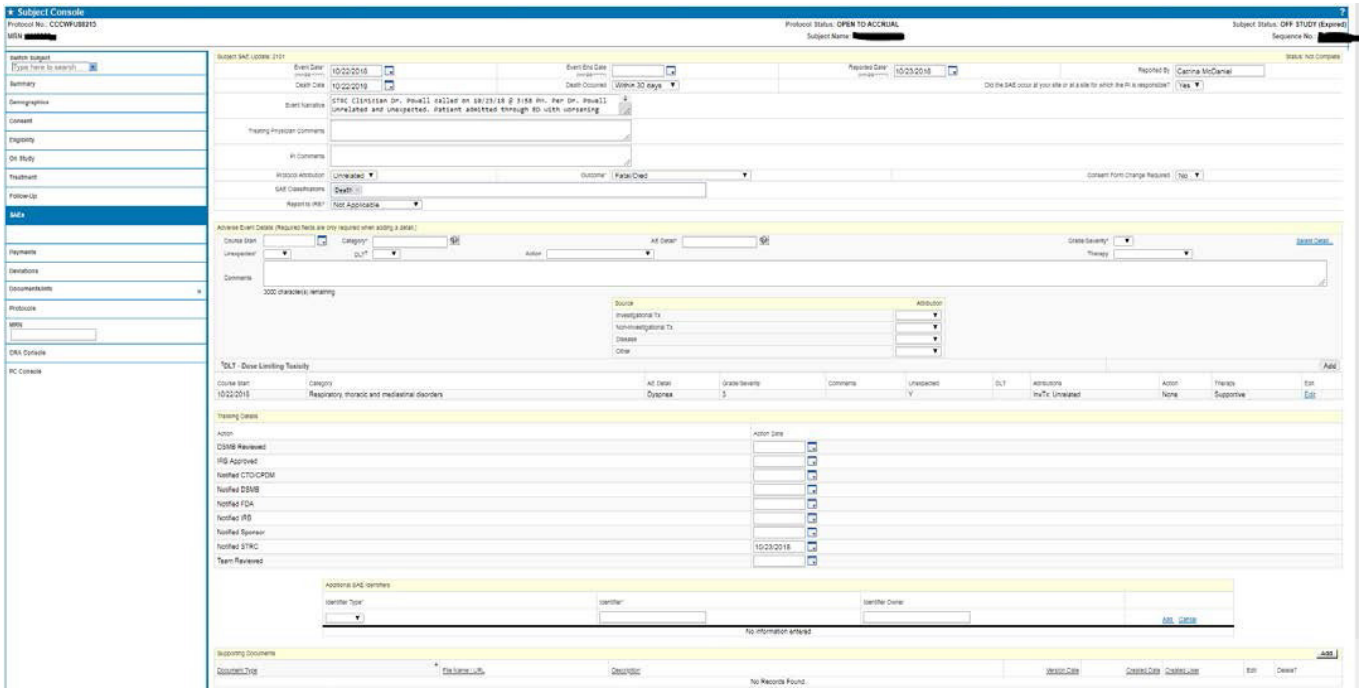

Screen Shot 2:



Screen Shot 3:




Screen Shot 4:



# Appendix E – Adverse Event Log

**WFBCCC Adverse Event (AE) Log**

**PI: _____ Subject PID: _____** **MRN: _____**

**Cycle #: _____** **Cycle Start Date: _____** **Cycle Start Time: _____** **Cycle End Date: _____** **Cycle End Time: _____**

| **Adverse Event CTC Term** | **Lab Value** | **Grade** (1-5) per CTC | **Start Date** | **End Date** | **Attribution** DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated | **Expected** N=No Y=Yes | **Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment | **Dose Limiting Toxitity (DLT)** N=No Y=Yes | **Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced | **Therapy Given** NO=None SYM=Symptomatic SUP=Supportive VSUP=Vigorous supportive | **Reportable?** IRB-IRB DSMC-DSMC FDA-FDA SPON-Sponsor (Mark all that apply) | **Adverse Event Report (AER) Filed** N=No Y=Yes | **Outcome** R=Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died | **Treating MD Initials/Date** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Radiation Pneumonitis | | | | | | | | | | | | | | |
| Radiation Fibrosis | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | |

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 5

DSMC- Safety and Toxicity Review Committee — Version 1/10/18

# Appendix F – 30 day Treatment Follow-up Form

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: M.D. Date: ___ ___/___ ___/___ ___

**Instructions:** Complete this form to follow-up with patients for adverse events.

**Name of Person Competing form_____**

**Did the subject have any adverse events in the last 30 days?** Yes ☐ No ☐
**If yes, please describe nature and grade of AE (Note*: If an SAE occurs in this period, report the event as required in Appendix D):**

_____
_____
_____
_____
_____
_____

**Was the subject removed from the study by the PI?** Yes ☐ No ☐

**Did the subject withdraw from the study?** Yes ☐ No ☐

**Did the subject complete the full course of SBRT and take the study drug?** Yes ☐ No ☐

# Appendix G – Current Medications Form

**Study Number: ___ ___ ___ ___ ___ PID: ___ ___ ___ ___ ___ ___ ___ ___**

**PI: _____ Date (mm/dd/yyyy): ___ ___/___ ___/___ ___ ___ ___**

**Instructions:** Fill this form out at the baseline/pre-study

**Study Visit:**
☐Baseline ☐ 3 mo. Post SBRT ☐ 6 mo. Post SBRT ☐ 9 mo. Post SBRT ☐ 12 mo. Post SBRT
Has the patient taken steroid medications in the last 3 months? (Y/N)
Has the patient ever taken any medications that fall within the class of bisphosphonates or rank ligand inhibitors? (Y/N)
If Y, list dose/frequency_____ and treatment dates _____

## Current Medications List

**Prescription Medications:**

| Name of Medication | Dose | Units | Frequency | Condition Medication Taken For | Start date (mm/dd/yy) | Stop date (mm/dd/yy) | Formulation | Route | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |
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# Appendix H – Medication administration form

Date/Time of drug administration: _____

Pharmacist distributing medication: _____

# Appendix I – Off-Study Form

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator:, M.D. Date: __ __/__ __/__ __

**Instructions:** Complete this form if the patient either withdraws consent or is removed from the study.

**Name of Person Competing form_____**

**Did the subject meet eligibility criteria for study enrollment?** Yes ☐ No ☐

**Was the subject removed from the study per physician decision?** Yes ☐ No ☐
(if yes, move to #5)

**Did the patient withdraw consent to participate in the study?** Yes ☐ No ☐
(if yes move to #1)

**Reason for patient withdrawal:**

1. ☐ Unacceptable toxicity from DRUG(s)
2. ☐ Did not want to participate anymore. Reason:
   _____
3. ☐Other: _____
4. Please specify what portion of the study the subject wishes to withdraw from:
   ☐ For just the DRUG(s) administration only
   ☐ For all components of the research study (including follow up in the medical record)

**Reason(s) for Removal:**

5. ☐ Patient exhibited progression of disease
6. ☐ Unacceptable toxicity from DRUG(s)
7. ☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest (*Describe below)
8. ☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible (*Describe below)
9. ☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment (*Describe below)
10. ☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits (*Describe below)
11. ☐ Termination of the clinical trial by the clinical sponsor

**Comment:**
If reason for withdrawal includes #7, 8, 9, or 10 then please add comments clarifying this information)_____

# Appendix J – ECOG KPS Conversion

## ECOG-KPS Conversion

| ECOG | KARNOFSKY |
|---|---|
| **0: fully active,** able to carry on all predisease performance without restriction. | **100% - Normal;** no complaints; no evidence of disease.<br><br>**90% - Able to carry on normal activity;** minor signs or symptoms of disease |
| **1 – Symptomatic but completely ambulatory** (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work) | **80 %- Normal activity with effort**; some signs or symptoms of disease.<br><br>**70% - Cares for self;** unable to carry on normal activity or to do active work |
| **2 – Symptomatic, <50% in bed during the day** Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours) | **60% - Requires occasional assistance**, but is able to care for most of his personal needs.<br><br>**50 %- Requires considerable assistance** and frequent medical care. |
| **3 – Symptomatic, >50% in bed, but not bedbound** (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours) | **40% - Disabled;** requires special care and assistance.<br>**30% - Severely disabled;** hospital admission is indicated although death not imminent. |
| **4 – Bedbound** (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) | **20% - Very sick;** hospital admission necessary; active supportive treatment necessary.<br>10% - Moribund; fatal processes progressing rapidly. |
| **5 – Death** | **0 - Dead** |

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# Appendix K – Toxicity Modified CTCAE Grading for Chest Wall Pain

To be completed by study nurse

Person completing study form:
Printed: _____ Signature: _____
Follow up at ___ mo after completion of SBRT

| Modified CTCAE v. 5 Chest Wall Pain Grading Scale | | | | | | |
|---|---|---|---|---|---|---|
| CTCAE Term *(Check to indicate score)* | None ☐ | Grade 1 ☐ | Grade 2 ☐ | Grade 3 ☐ | Grade 4 ☐ | Grade 5 ☐ |
| Descriptor | None | Mild pain not requiring any intervention | Moderate pain at relieved completely or to tolerable levels by NSAIDs, or pain that is limiting instrumental ADLs without NSAIDs | Moderate pain relieved completely or to tolerable levels by narcotic medications or gabapentin, that is otherwise limiting instrumental ADLS without narcotics or gabapentin | Debilitating pain that is not controlled by NSAIDS, narcotics, or gabapentin, or pain that requires nerve block. Or pain that is not controlled by any intervention. | Not applicable |

# Appendix N –Radiation Treatment Details

To be completed by the treating physician following completion of treatment planning.

Completed by _____

Date _____

| For the Current Radiation Plan | | | | |
|---|---|---|---|---|
| **Radiation Prescription Dose (Gy)** | **# of Fractions** | **V20 Lungs minus GTV (%)** | **Maximal point dose to rib bone (Gy)** | **Volume (cc) of chest wall contour receiving > 30 Gy** |
| | | | | |

If prior radiation treatment to the thorax, including prior treatment for breast cancer
Construct an EQD2 composite plan if possible and prior records are available

Dates of start and completion of prior radiation plan _____ to _____

Site of prior RT: _____

If lung, note anatomic side and lobe: _____

If breast, note inclusion or exclusion of regional nodal volumes:_____

Composite V20 lungs minus current plan GTV on EQD2 using a/b 3: _____(%)

Composite EQD2 using a/b 3 maximal point dose to the chest wall: _____ (Gy)

# Appendix O – Cortical Thickness Change

To be completed by the treating physician following completion of all data collection.

Routine CT DICOM images will be stored in PACS imaging system in the electronic medical record indefinitely. Following conclusion of the study, the following information will be assessed utilizing cortical thickness mapping procedures with treatment planning simulation CT images, radiation dosimetric plans, and routine follow up CT scans. The chest wall contour will be defined as a 2 cm expansion from the lung parenchyma from the costovertebral angle to the sternum. Cortical thickness maps will be created for all CT scans. For each patient the following information will be collected.

| **Baseline Mean C.Th within planned 50% isodose line** | | |
|---|---|---|
| | | |
| | **Mean C.Th with the region of bone receiving at least 30 Gy** | Diff (%) |
| 3 mo. | | |
| 6 mo. | | |
| 9 mo. | | |
| 12 mo | | |

| **Baseline Mean C.Th within planned 50% isodose line** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| **Mean C.Th within each region of bone receiving dose at 10 Gy intervals** | | | | | | | | | | |
| | 0 - 10 Gy | Diff (%) | >10 Gy - 20 Gy | Diff (%) | >20 Gy - 30 Gy | Diff (%) | >30 Gy - 40 Gy | Diff (%) | > 40 Gy | Diff (%) |
| 3 mo. | | | | | | | | | | |
| 6 mo. | | | | | | | | | | |
| 9 mo. | | | | | | | | | | |
| 12 mo | | | | | | | | | | |

## Appendix P – Urinary NTX Measurement

To be completed following completion of all specimen and protocol data collection.

| Time point | **UTX/Cr ratio** nM BCE/ mmol Cr (normalized) |
|---|---|
| Baseline | |
| 3 mo | |
| 6 mo | |
| 9 mo | |
| 12 mo | |

## Appendix Q – Fracture Incidence

| Time point | Bone Fracture (Y/N)<br>Described in CT report<br>Located within treatment field<br>(50% Isodose line) |
|---|---|
| Baseline | |
| 3 mo | |
| 6 mo | |
| 9 mo | |
| 12 mo | |

*Fracture incidence is determined by the treating radiation oncologist utilizing direct examination of the CT images compared side by side with the treatment plan. The isodose lines can be easily inspected on the treatment plan utilizing planning software to correlate followup imaging with the area treated. If there is any question of the proximity of the fracture to the treated region, followup images can be fused together with the treatment plan images for exact correlation. Rib fractures are generally easy to see by direct inspection of the CT images and if present are also typically commented on in the body of the CT report. If bone fracture is not described in the CT report, it can be assessed by the radiation oncologist.

# Appendix R - Urine Collection and Delivery to Storage in – 80 C freezer

Person collecting urine sample _____ Date _____

Delivered to storage in – 80 C freezer