A Prospective Randomized Phase II Study of 1 vs 2 Fractions of
Palliative Radiation Therapy for Patients with Symptomatic Bone Metastasis
Comprehensive Cancer Center of Wake Forest University (CCCWFU)
CCCWFU # 01416

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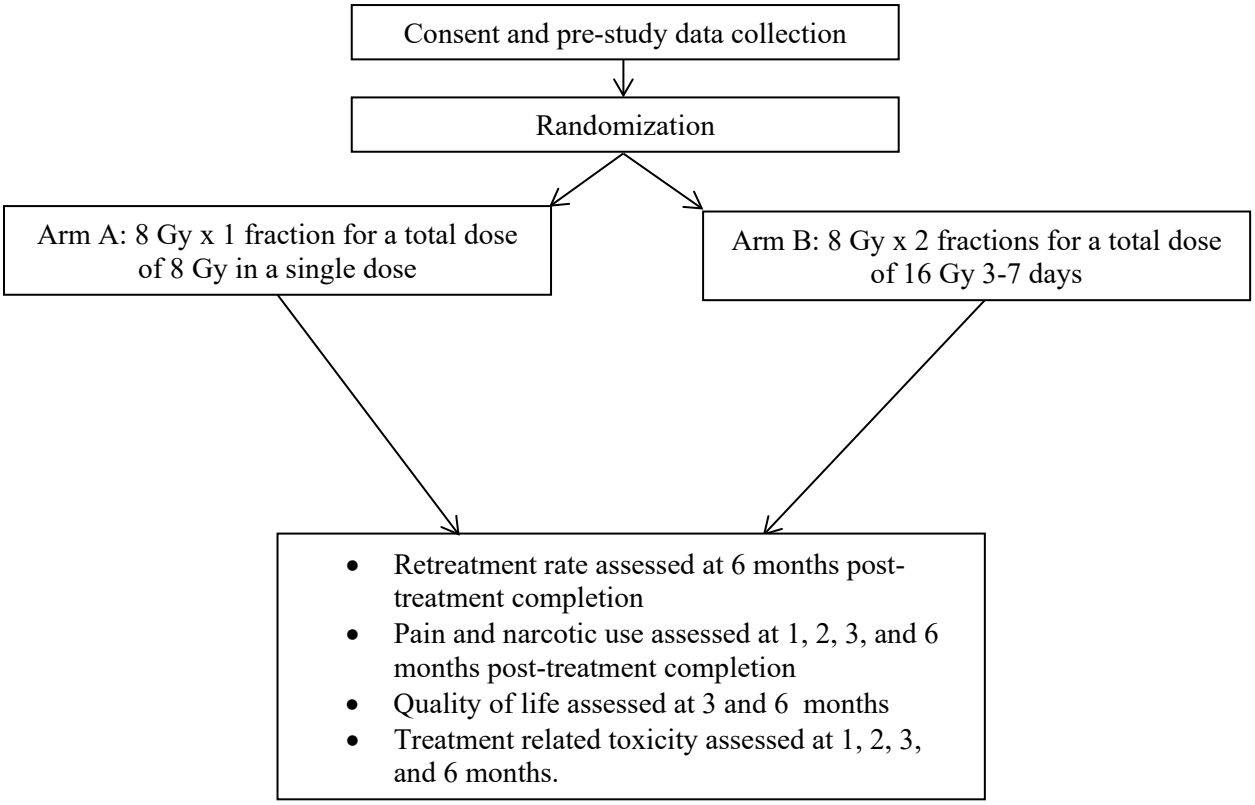

Consent and pre-study data collection
Randomization
Arm A: 8 Gy x 1 fraction for a total dose of 8 Gy in a single dose
Arm B: 8 Gy x 2 fractions for a total dose of 16 Gy 3-7 days
Retreatment rate assessed at 6 months post-treatment completion
Pain and narcotic use assessed at 1, 2, 3, and 6 months post-treatment completion
Quality of life assessed at 3 and 6 months
Treatment related toxicity assessed at 1, 2, 3, and 6 months.

1.0 Introduction and Background

Bone metastases are not only the most common cause of cancer-related pain, but palliative radiotherapy is prescribed most frequently to relieve symptoms. External beam radiotherapy (EBRT) is a well-established and efficacious method of palliating painful bone metastases (1). Numerous randomized trials have evaluated the potential benefits of certain dose fractionations of EBRT (1–7), yet controversy remains over the optimal treatment schedule. For example, RTOG 97-14 randomized 898 patients with breast or prostate cancer to receive 8 Gy in 1 fraction or 30 Gy in 10 fractions. There was no significant difference in complete or partial pain relief at 3 months. Patients in the single dose group had a significantly higher retreatment rate at 3 months (18% vs. 9%) but a statistically lower toxicity rate (10% vs 17%) (8). An economic analysis of this trial calculated quality-adjusted life year survival to be 7.3 months vs 9.5 months in the two treatment arms. The authors concluded that single fraction was less expensive and more cost-effective (9). Chow et al conducted a systematic review and meta-analysis of randomized palliative radiotherapy trials comparing single fractions to multiple fractions. Twenty-five randomized trials were identified with no significant differences in pain response rates. The likelihood of re-treatment was 2.6-fold higher (95% CI, 1.92-3.47; P < 0.00001) in single fraction EBRT arm patients (10).

1.1 Rationale for Proposed Treatment Dose and Schedule

The protocol attempts to further define the results of RTOG 97-14, which demonstrated that 8 Gy x 1 was equal to 30 Gy in 10 fractions for the majority of clinical endpoints. The primary exception was the rate of retreatment, where 8 Gy x1 was shown to require additional therapy. In this study, we are investigating if a second fraction given within 7 days of the first fraction, reduces the retreatment rate or improves pain control.

2.0 Objectives

2.1 Primary Objective

2.1.1 To determine whether 8 Gy x 2 fractions results in lower cumulative re-treatment rates at 6 months post-treatment completion compared to 8 Gy x 1 fraction in solid tumor patients with bone metastases.

2.2 Secondary Objectives

2.2.1 To determine whether 8 Gy x 2 fractions provides superior pain at 3 and 6 months post-treatment completion compared to 8 Gy x 1 fraction in solid tumor patients with bone metastases.

2.2.2 To determine whether 8 Gy x 2 fractions is associated with improved quality of life at 3 and 6 months post-treatment completion compared to 8 Gy x 1 fraction in solid tumor patients with bone metastases.

2.2.3 To determine if 8 Gy x 2 fractions is associated with increased toxicity.

2.2.4 To correlate patient satisfaction, perceived stress, and social support assessed via self-reported outcomes with treatment outcomes.

2.3 Exploratory Objective

2.3.1 To determine whether use of a bone strengthening agent is associated with improved pain relief, decreased narcotic usage, and re-treatment rates.

2.3.2 To assess the impact of pain response after radiotherapy on bone structural properties such as bone mineral density and cortical thickness

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Diagnosis of cancer, not including multiple myeloma or lymphoma/leukemia.

3.1.2 Radiographic evidence* of bone metastases within 8 weeks of study for non-weight bearing sites and 4 weeks for weight bearing sites. The patient must have pain which appears to be related to the radiographically documented metastasis in the opinion of the treating physician, and the decision has been made by the responsible clinician that a course of palliative external beam radiation therapy is appropriate treatment. Multiple sites eligible if they can be included in no greater than 3 treatment sites and not all identifiable lesions will require treatment unless they are painful lesions
**This should be one of the following: Plain Film, Bone Scan, PET scan, CT scan, or MRI.*

3.1.3 The involved bone(s) is/are orthopedically stable and not in need of stabilization via either definitive RT, surgical intervention, or both.

3.1.4 Eligible Treatment Sites Are:
Weight bearing sites
1. pelvis *(excluding pubis)*
2. femur
3. sacrum and/or sacroiliac joints
4. tibia
5. up to 5 consecutive cervical, thoracic or lumbar vertebral bodies
6. lumbosacral spine

Non-weight bearing sites
7. up to 3 consecutive ribs
8. humerus
9. fibula
10. radius ± ulna
11. clavicle
12. sternum
13. scapula
14. pubis
15. skull
16. bones of hands or feet

If multiple sites are treated, the treatment site is included as weight-bearing if any of the sites include the pelvis, sacrum, femur or tibia.

3.1.5 Pain score of at ≥5 on a scale of 0 – 10 within a week of enrollment OR pain score < 5 with ≥ 60 mg of morphine (or equivalent) per day.

3.1.6 ECOG performance status of 0 - 3.

3.1.7 Ability to understand and the willingness to sign an IRB-approved informed consent document.

3.1.8 Negative pregnancy test at study registration.

3.1.9 Life expectancy of at least 12 weeks as deemed by the treating oncologist.

3.1.10 Patients will be eligible for treatment of multiple synchronous osseous sites only if those sites can be included in no more than three treatment sites. For patients with painful metastases that are contiguous but do not fit into the definition of a site listed above, those patients will still be eligible but will be considered to have two treatment sites. For example, a patient with a lesion of T4, T7 and T9 would be eligible but would be considered as two treatment sites since more than five consecutive vertebral bodies would be treated. These lesions could be treated with one field, even though the treatment is coded as two sites.

3.2 Exclusion Criteria

3.2.1 Previous radiotherapy or palliative surgery to the painful site that is planned for treatment.

3.2.2 Spinal cord or cauda equine compression/effacement in vertebral metastases with neurological symptoms other than just pain for the lesion that is planned for treatment.

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 CCCWFU population estimates, we expect approximately 40% of participants to be women. Translating this to our sample size estimate of 158, we plan to enroll at least 63 women.

We do not expect the percentage of Hispanic/Latino or racial minority cancer patients eligible for this study to be higher than the percentage of Hispanic or racial minority new cancer patients seen at CCCWFU (2.2% and 13.3%, respectively); therefore, we plan to enroll at least 21 racial minority and 3 Hispanic/Latino patients.

Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Methods

4.1 Study Design

We will use a prospective randomized study design for recruiting patients with painful bone metastasis at the CCCWFU. Pain will be assessed prior to randomization. Patients will be randomized between 1 or 2 fractions of 8 Gy. The randomization will occur after registration; patients will be randomized equally between the two treatment arms. Treatment needs to begin within 14 days of registration. All baseline data needs to be collected before treatment. Quality control, such as valid values, range checks and between-variable consistency will be performed at time of data entry. Data will be kept secure with password protection.

4.2 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into ORIS Screening Log 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. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. 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 [redacted]
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. 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
- register the patient on the study

4.3 Data Collection

At the time of enrollment, a detailed history and physical exam will be performed, including abstraction of patient vital signs and also documenting co-morbidities, patient demographics, age, gender, other medical conditions, and tumor characteristics. Other variables, such as education level, type of health insurance, and marital status (married/single/widowed/divorced/other) will also be obtained.

Blood Collection: Patients may consent to provide optional blood samples to be used for future genomic studies at baseline.

Prior Cancer Therapy: Information regarding the patient's history for anti-cancer therapy will be recorded.

Use of Bisphosphonates/Denosumab: Information regarding the patient's history for the use of biphosphonates will be recorded. This will include the specific agent, dose, and date treatment started.

Changes in systemic chemotherapy, hormonal therapy, immunotherapy or the use of bisphosphonates for 4 weeks before and after the delivery of radiotherapy are allowed and will be recorded.

Pain level and Pain Medications: The patient's pain level will be assessed using the NRPS (detailed below). Information regarding the patient's history for the use of pain medications will be recorded. This will include the specific agent, dose, and date treatment started.

Nutrition Status, vitals, BMI: At each encounter, height (at baseline only), weight, Body Mass Index (BMI=kg/M^2), and history of weight loss within three months prior to enrollment until patient's study completion will be recorded and/or extracted from patient records.

ECOG Performance Status

Patient Self-Reported Outcomes (SRO):
For evaluation of pain relief, the Numerical Rating Pain Scale (NRPS; Jensen 1999) will be used. The NRPS is a simple measure of pain on an 11-point scale (0-10). In the study comparing the reliability and validity of several measures of pain intensity, the composites of 0-10 ratings have been shown to be useful when maximal reliability was necessary in studies with relatively small sample sizes or in clinical settings in which monitoring of changes in pain intensity in individuals is needed. This will be performed prior to treatment and again at 1, 2, 3, and 6 months.

For patients with a pain score >4 in the treated area at the 3 and 6 month follow-up, imaging (plain film, CT, bone scan, MRI) is recommended to assess for bone stability and pathologic fractures. Imaging should correlate with other imaging ordered by other treating physicians when possible. Coordination of all treatment and imaging should be collaborative to ease patient burden.

We will also include the following psychosocial measures at baseline and again at 3 and 6 months:

- European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL
- Patient Satisfaction with Cancer Care (11)
- Perceived Stress Scale (12)
- Social Support (13)

Measurement of Treatment-Related Toxicities: Adverse events will be evaluated by the NCI Common Terminology Criteria for Adverse Event (CTCAE), v. 4.0. (14). Because of the patient population as well as the treatment, emphasis will be placed on gastrointestinal (GI disturbance, esophagitis, diarrhea, nausea, and vomiting), hematological (low blood counts or bleeding), spinal (bone fracture, compression fracture, insufficiency, or myelitis), and pulmonary toxicities (pneumonitis). However, all adverse events recorded by clinical research coordinators will be analyzed. Given the variety of non-protocol related treatment, toxicity will be assessed at 30 days after protocol treatment, as per DSMC requirements. These will be documented in Appendix I.

Focused Late AE Assessments: At 2, 3 and 6 months post-treatment, a focused AE assessment dependent upon the specific body area treated will be performed. These will be documented in Appendix I. Specific AEs to be collected will include the following:

a) Fistula formation
    a. Abnormal opening in the passageway from mouth to stomach (esophagus), bowels or bladder
b) Scarring of the small or large bowel resulting in a blockage in the bowel that would require treatment
c) Fracture of the bone within the radiotherapy treatment field (Fractures may require surgical treatment to prevent permanent disability).
d) Temporary or permanent damage to the spinal cord, resulting in:
    a. Skin sensations, such as burning, prickling, itching, or tingling
    b. Muscle weakness causing inability to walk (paralysis)
    c. Decreased ability or loss of ability to move a body part or to hold urine or control a bowel movement

Imaging: The patient will undergo CT-Simulation prior to treatment. If deemed necessary by the treating physician at the time, follow-up imaging is allowed at 3- and 6-months after treatment. These scans, if performed, will be as part of standard of care, particularly in the setting of increased pain at post-treatment evaluations (see above). Imaging data obtained from these scans will be collected for the purposes of the exploratory objective (Section 2.3).

4.4 Radiation Therapy

4.4.1 Treatment Plan
Arm 1: 8.0 Gy x 1 fraction.
Arm 2: 8.0 Gy x 2 fractions to 16.0 Gy total dose with 3-7 days in between.

4.4.2 Patient Positioning and Simulation: Patients must be positioned in a stable supine or prone position at the treating physician's discretion. Any immobilization techniques can be used for 3D conformal therapy at the treating physician's discretion. For cervical spine or cervicothoracic junctional areas, a head and neck immobilization device is preferred. Simulation of treatment fields is required prior to the treatment.

4.4.4 3D Treatment CT simulation is required. Non-coplanar beams can be employed. Multiple beam directions can be used. Target volume should covered by more than or equal to 90% of the prescription dose.

4.4.5 Simulation of treatment fields is required prior to the first treatment. Prior to the first treatment, there must be an approved simulation or portal film documenting that the treatment site is adequately covered and approved by a radiation oncologist.

4.4.6 Treatment machine requirements. Treatment must be given using megavoltage equipment with 4-20 MV photons or 5-20 MeV electrons. The minimum Source-Axis Distance *(SAD)* shall be 80 cm.

4.4.7 For spine lesions, treatment volume will include the entire vertebral body(s) of the involved spine, plus one vertebral body superior and one vertebral body inferior to the index spine. A treatment field margin of 1-2 cm laterally beyond the vertebral body(s) can be used based on the treating physician's discretion. For non-spine lesion, treatment volume will general include the lesion as identified on imaging studies with 1-2 cm margin. Final treatment volume will be at treating physician's discretion.

4.4.8 Rib metastases may be treated with electrons or with photons. When electrons are used, the appropriate energy should be chosen such that the entire lesion is covered by the 90% *(or higher)* isodose curve. The dose will be prescribed to the 100% isodose line.

When photons are used, parallel opposed fields may be used, with the depth prescribed to the mid thickness. Oblique/tangential fields for rib metastasis are strongly encouraged to avoid treatment of underlying structures. A single field may be used to cover the lesion, with the depth set at the estimated depth of the rib lesion, and the dose prescribed to that level.

4.4.9 When more than one osseous site is to be included into one treatment field, the treating radiation oncologist may use differing field arrangements at her/his discretion, with the fields arranged to provide relatively uniform treatment of the target sites with a minimum of uninvolved normal tissues.

4.4.10 For patients who receiving 8 Gy x 2 to an area near or involving either the spinal cord or cauda equina, the spinal cord and cauda equina needs to be contoured. The dose to the countered cord/cauda equina this this region will be limited to 107% of the prescribed dose. If needed, the PTV coverage can be lowered to 85%. If PTV coverage is between 85% and 80%, a minor deviation should be reported. If PTV coverage is below 80%, a major deviation should be reported.

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 Cumulative re-treatment rates by treatment arm assessed at 6 months post-treatment completion.

5.2 Secondary Outcomes

5.2.1 Pain, on a 0-10 scale, and narcotic use, in daily oral morphine equivalents, by treatment arm assessed at 3 and 6 months post-treatment completion.

5.2.2 Quality of life by treatment arm, assessed by QLQ-C15-PAL at 3 and 6 months post-treatment completion.

5.2.3 Toxicity by treatment arm, assessed by CTCAE version 4.0.

5.2.4 Association between patient satisfaction, perceived stress, and social support assessed via self-reported surveys and treatment outcomes.

5.3 Exploratory Outcome

5.3.1 Association of use of a bone strengthening agent with improved pain relief, decreased narcotic usage, and re-treatment rates.

5.3.2 Association of pain response after radiotherapy on bone structural properties such as bone mineral density and cortical thickness.

6.0 Treatment Plan

6.1 Study-Related Activities

	Screening/ Baseline[a]	Pre-Treatment[h]	At Each Treatment	1 Month Post Treatment Completion[f,g]	2 Months Post Treatment Completion[f,g]	3 Months Post-Treatment Completion[f,g]	6 Months Post-Treatment Completion[f,g]
Informed Consent	X						
Demographics: age, gender, education, health, insurance, marital status	X						
Medical history, tumor characteristics	X						
Performance Status (ECOG)	X					X	X
B-HCG[b]	X						
Blood Collection (optional)		X				X[f,l]	
Nutritional status, BMI[i]	X		X			X	X
Vital Signs	X					X	X
Radiologic assessment	X[c]					X[e,m]	X[e,m]
Patient Questionnaires[d]		X				X	X
Concomitant Medications	X		X	X	X[k]	X[k]	X[k]
Adverse event evaluation			X	X	X[j]	X[j]	X[j]
NRPS Pain Scale	X			X[g]	X[g]	X[g]	X[g]

a. Pre-study requirements listed in table must be completed **within** 14 days prior to registration unless otherwise noted.
b. Serum pregnancy test (women of childbearing potential).
c. Within 8 weeks of registration for non-weight bearing sites and 4 weeks for weight bearing sites
d. See Appendix G.
e. Imaging ordered by the treating physician according to the standard of care, only if indicated. CT scan is not required to be performed for study purposes at follow up, but any CT scans obtained as standard of care will be used for purposes of reviewing changes in cortical thickness as an exploratory aim.
f. To be completed 3-6 weeks from final treatment date (1 month visit), 7-9 weeks from final treatment date (2 month visit), 10-18 weeks from final treatment date (3 month visit) and 20-34 weeks from final treatment date (6 month visit).
g. For patients who are undergoing additional therapy of any kind and are being followed by another treating physician, the follow-up visit can be deferred to that treating physician. Schedule of follow-up may be deferred to that treating physician and activities will be captured when they fall within visit windows. Toxicity (AEs), pain (NRPS), and patient questionnaire can be done over the phone +/- 5 days of said visit.
h. To be completed any time after consent is signed, but prior to treatment. Not needed for registration.
i. Height will be captured at the Pre-Study/Baseline visit only.
j. Focused AE assessment according to those specified in Section 4.3 and outlined in Appendix I (2-, 3- and 6- month assessment).
k. Focused ConMed assessment; collected medications related to bone pain and bone-strengthening agents only (bisphosphonates, RANK-L inhibitors, parathyroid hormone analogs/modulators/agonists).
l. Optional blood collection for follow-up must occur at 3 months if consented to by the subject (See Section 9.0).
m. Appendix K to be completed at the time of Data Reconciliation.

6.2 Treatment Administration

Arm A: 8.0 Gy x 1 fraction to 8.0 Gy total dose.
Arm B: 8.0 Gy x 2 fractions to 16.0 Gy total dose. The two fractions will be separated by 3-7 days.

Simulation of treatment fields is required prior to the first treatment. There must be imaging of treatment verification approved by a radiation oncologist. All fields must be treated each day. Treatment volume will include the radiographic abnormality with at least a 2 cm margin. Treatment of the entire bone is not required.

6.2.1 Retreatment

Previous studies have shown that pain relief from radiotherapy may take several weeks to become apparent. Therefore, patients should not be re-irradiated to the same treatment site for at least 4 weeks after completion of treatment on this study unless the patient has an increase of 2 points on the worst pain score above the nadir or a 25% increase in daily dosage morphine equivalent of pain medication. Dose and fractionation schemes are left to the discretion of the treating radiation oncologist. Cumulative retreatment occurrence will recorded at the 6 month follow-up visit.

6.3 Duration of Therapy

This is a study of 1 vs. 2 fractions of radiation therapy. For the patients randomized to receive 2 fractions, the treatment may continue unless one of the following criteria applies:

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- 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

Given the variety of non-protocol related treatment, toxicity will be assessed at 30 days after protocol treatment as it is anticipated that this would be part of standard of care for such treatment, and per DSMC requirement. For patients not receiving any additional treatment, additional follow-up visits will occur at 3 and 6 months with follow-up radiologic assessment at the discretion of the treating physician if pain score is >4 as such is standard of care for patients who receive the treatment.

For patients who are undergoing additional therapy of any kind and are being followed by another treating physician, follow-up can be deferred to that treating physician. Toxicity and pain can be assessed via chart review and over the phone for these patients at the appropriate study time points. Patients will be followed in this same manner if being treated at an outside facility. Patients who experience adverse events will be followed every 3-6 weeks until stabilization of the adverse event or until 6 months post-treatment, whichever occurs first.

A patient may remain in the study until one of the following criteria applies:

- Patient decides to withdraw from the study, or

- The patient has completed a minimum of 6 months follow-up.
- Patient enters End of Life Hospice Care and will no longer be followed routinely.

7.0 Measurement of Effect

7.1 Pain Response

Assessment of pain should be on a scale of 0 to 10, with boundaries of 0 representing no pain and 10 representing maximal pain. Pain should be assessed by only the worst pain score for the previous 3 days.

Complete response: A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent.

Partial response: reduction of 2 or more points (0-10 point scale) without analgesic increase OR analgesic reduction of 25% in daily oral morphine equivalent without increase in pain.

Pain progression:

- Increase in pain score of 2 or more above the nadir at the treated site with stable daily oral morphine equivalent, or
- An increase of 25% or more in daily oral morphine equivalent compared with baseline with the pain score stable or 1 point above baseline

Indeterminate response: Any response that is not captured by the complete response, partial response, or pain progression definitions

All patients with a pain score > 4 in the treated area at the 3-month follow-up will have plain radiographs to assess for bone stability and pathologic fractures.

Any patient with progressive pain in the treated area should have radiographs of the area to assess for bone stability and pathologic fracture.

7.2 Radiation Induced Bone Changes

The patient will undergo standard of care CT simulation prior to treatment. No further imaging is required by the protocol. If the patient undergoes CT imaging after treatment for any reason, imaging will be analyzed for quantitative assessment of radiation-induced bone changes including bone mineral density and cortical. The date and type of imaging (if applicable) will be collected if it falls within the timeframes delineated in the follow-up assessment calendar (Section 6.1, attention to Footnote f). The scan data will be used for analyses comprising the exploratory objective delineated in Section 2.3. These results, if applicable, will be documented on **Appendix K** by the researches after completion of the study.

8.0 Adverse Events List and Reporting Requirements

8.1 Adverse Event List for Radiation Treatment

Expected side effects, depending on the area treated, include nausea, vomiting, diarrhea, skin erythema and alopecia in the irradiated area, esophagitis, myelosuppression, urinary urgency and frequency, and pneumonitis.

8.2 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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'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.

8.3 DSMC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. All Adverse Events that occur during protocol intervention 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.

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.

8.4 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.

9.0 Blood Collection for Translational Research and Tissue Banking

In this study, if the patient consents, plasma and whole blood will be collected at baseline and post-treatment (3 months). We will explore promising genetic basis biomarkers with regard to of cancer-induced bone pain and cachexic syndrome following bone metastatic disease, since much work still remains to be accomplished in this area.

The whole blood collected will be utilized for microarray analyses or next generation RNA sequences. The pre-treatment and post-treatment (3 months) of plasma will be tested for a number of cytokines and proteins (e.g. calcitonin-gene related peptide (CGRP), substance P (SP), angiotensin II, Ang 1-7) that are thought to be predictive of cancer-induced bone pain and cachexic syndrome following bone metastasis disease.

This may lead to identification of promising new biomarkers with the goals of
1. Identifying factors predictive of outcome such that patients may be better stratified in future trials;
2. Developing novel treatment strategies which target the molecular abnormalities identified.

1) Blood Sample Preparation

1. Email notification will be sent to [redacted] the day before the blood collection.

2. Blood will be collected in green-top lithium-heparin or sodium-heparin vacutainer tubes (1 x 10 ml tube), and immediately inverted 8-10 times to prevent coagulation. **Attention: Protocol #: CCCWFU # 01416 should be on the tube**

3. Samples will then be sent to Dr. Shiozawa's lab (Hanes 4013) for research use. Dr. Shiozawa's lab [redacted]

4. Upon receipt, tubes will be centrifuged at 200 x g for 10 mins at room temperature with the break off.

5. Plasma will be removed and placed in 1.5ml Eppendorf tubes and transferred to the Shiozawa lab and stored in -80 freezer until further processing. .

6. Buffy coat will be collected and placed in Eppendorf tubes in RNA later and transferred to the Shiozawa lab, and stored in -80 freezer until further processing.

10.0 Data Management

Informed consent document	Wiser
Appendix A: Protocol registration form	Wiser
Appendix B: Subject Eligibility Checklist	Wiser
Appendix C: Race & Ethnicity Verification	Wiser
Appendix D: Mandatory DSMC SAE Reporting Guidelines	Wiser
Appendix E: Baseline data collection form	REDCap
Appendix F: Treatment data collection	REDCap
Appendix G: Patient Questionnaire	REDCap
Appendix H: Numerical Rating Pain Scale (NRPS)	REDCap
Appendix I: Adverse Events	Epic/REDCap
Appendix J: Retreatment Data Form	REDCap
Appendix K: Radiation Induced Bone Changes	REDCap

11.0 Statistical Considerations

11.1 Analysis of Primary Objective

This is a randomized Phase 2 study, with the primary objective to compare the 6-month cumulative incidence of re-treatment rates between groups. Based on previous research, the 8 Gy x 1 fraction [8/1] group (control group) had a retreatment rate of 18% (RTOG Study 97-14). The primary analysis will use a one-sided log-rank test statistic to test the null hypothesis that the re-treatment rates are equal in each group versus that alternative that the re-treatment rates are lower in the 8 Gy x 2 fractions [8/2] group. This analysis will account for competing risks such as death. Analyses will be performed on the patient level, thus if a patient has multiple metastases and any one of these requires retreatment then the patient will be considered retreated.

11.2 Analysis of Secondary Objective

There are several secondary outcomes of interest in this study. Most of these are measured on a continuous scale (i.e., quality of life by QLQ-C15-PAL, Patient satisfaction with cancer care, perceived stress scale) and thus will be compared between groups using 2-sample t-tests. In addition, the variable for pain response is categorical rather than continuous and will be compared at 3-months between groups using a Fisher's exact test. Patients categorized as Complete or Partial Responders will be compared with those categorized as stable or worsening pain responders.

Groups will also be compared to determine whether there are any differences in the number or severity of toxicities. When comparing severity of toxicities between groups, chi-square tests will be examined. The Cochran-Armitage trend test (in SAS Proc Freq) can be used to determine if there is evidence a trend in severity of toxicities when comparing groups.

In addition to the primary and secondary analyses described above, analyses will be performed that examine whether there are associations between quality of life, patient satisfaction and perceived stress measures and treatment outcome (re-treatment rates or amount of pain relief). In these

analyses, the outcome will be either re-treatment (yes/no) or amount of pain and predictors will include treatment arm, patient level measure and the treatment by patient level measure (i.e., QLQ-C15-PAL) interaction. For these analyses, either multiple logistic regression (for binary outcomes) models or analysis of covariance (ANCOVA) models for continuous outcomes will be used.

In these multiple logistic regression or ANCOVA models additional characteristics such as gender, whether the patient has weight-bearing (yes/no), ECOG performance status, number of lesions, or biophosphonates will also be considered as covariates in the models.

For the exploratory outcome of examining the association between the use of a bone strengthening agent with pain relief, narcotic use and re-treatment rates either two-sample t-tests (if pain is measured on a continuous scale) or Fisher's exact tests (for categorical measures) will be used. In addition multiple logistic regression or ANCOVA models will be fit to look at the an outcome (i.e., pain relief yes/no) and the impact of bone strengthening agents (yes/no), number of metastases (one/more than one), treatment group (8/1 or 8/2) and the treatment by bone strengthening interaction.

11.3 Power and Sample Size

Power calculations were performed using PASS 13. When accounting for competing risks, a one-sided logrank test with an overall sample size of 102 subjects (51 in the control group and 51in the treatment group) achieves 80% power at a 0.2 significance level to detect a hazard ratio of 0.5251. The study is expected to last for 42 months with an accrual (entry) time of 36 months and a follow-up time of 6 months after the last patient is accrued. The cumulative incidence proportions at time 3 months for the event of interest are 0.18 in the control group (8/1) and 0.10 in the treatment group (8/2). The cumulative incidence proportions at time 6 months for the competing risk factors are 0.20 in the control group and 0.20 in the treatment group. The proportion of subjects lost to follow-up during the entire study is conservatively estimated at 0.2.

11.4 Estimated Accrual Rate

It is anticipated that 3 patients a month will be accrued to this trial, thus the target of 102 patients should be met in approximately 36 months. .

11.5 Estimated Study Length

Since the primary analysis is based on 6 month re-treatment rates and we specify 6-months of follow-up for all patients, the protocol should be completed in 24months.

11.6 Interim Analysis Plan

An interim futility analysis is planned for this study. After 50 patients are enrolled (25 in each group) a test statistic will be calculated for z-test to compare groups using a two-proportion test. If the test statistic has a value of 1.5 (or larger) suggesting that there is evidence that the 8/2 group has a re-treatment rate that is worse than the 8/1 group, the trial will be considered to be stopped for futility. The conditional power, if this were to occur, would be 3.5%, suggesting the futility index would be 96.5%. This calculation was performed using PASS 13.

Logrank Tests Accounting for Competing Risks

Numeric Results for a One-Sided Test with T0 = 3 and W = 0.2

Power	N	Ctrl N1	Trt N2	Prop Ctrl p1	Hazard Ratio HR	Ctrl Main Event Incid Fev1	Trt Main Event Incid Fev2	Ctrl Comp Risks Incid Fcr1	Trt Comp Risks Incid Fcr2	Accr'l Time R	Follow Up Time T-R	Alpha	Rpt Row
0.80195	102	51	51	0.5	0.5251	0.1800	0.1000	0.2000	0.2000	18	6	0.200	1

Numeric Results for a One-Sided Test with T0 = 3 and W = 0.2 (Continued)

Beta	E	Ctrl E1	Trt E2	Total Prob Event Pr(ev)	Ctrl Prob Event Pr(ev1)	Trt Prob Event Pr(ev2)	Ctrl Event Hazard Rate hev1	Trt Event Hazard Rate hev2	Ctrl Comp Risks Hazard Rate hcr1	Trt Comp Risks Hazard Rate hcr2	Rpt Row
0.19805	27.5	16.8	10.8	0.3399	0.4138	0.2660	0.0755	0.0396	0.0839	0.0793	1

References

Machin, D., Campbell, M.J., Tan, S.B., Tan, S.H. 2008. Sample Size Tables for Clinical Studies, Third Edition. Wiley-Blackwell, Chichester, United Kingdom.
Pintilie, M., 2006. Competing Risks: A Practical Perspective. John Wiley & Sons, Chichester, United Kingdom.
Pintilie, M., 2002. 'Dealing with Competing Risks: Testing Covariates and Calculating Sample Size'. Statistics in Medicine, Volume 21, pages 3317-3324.

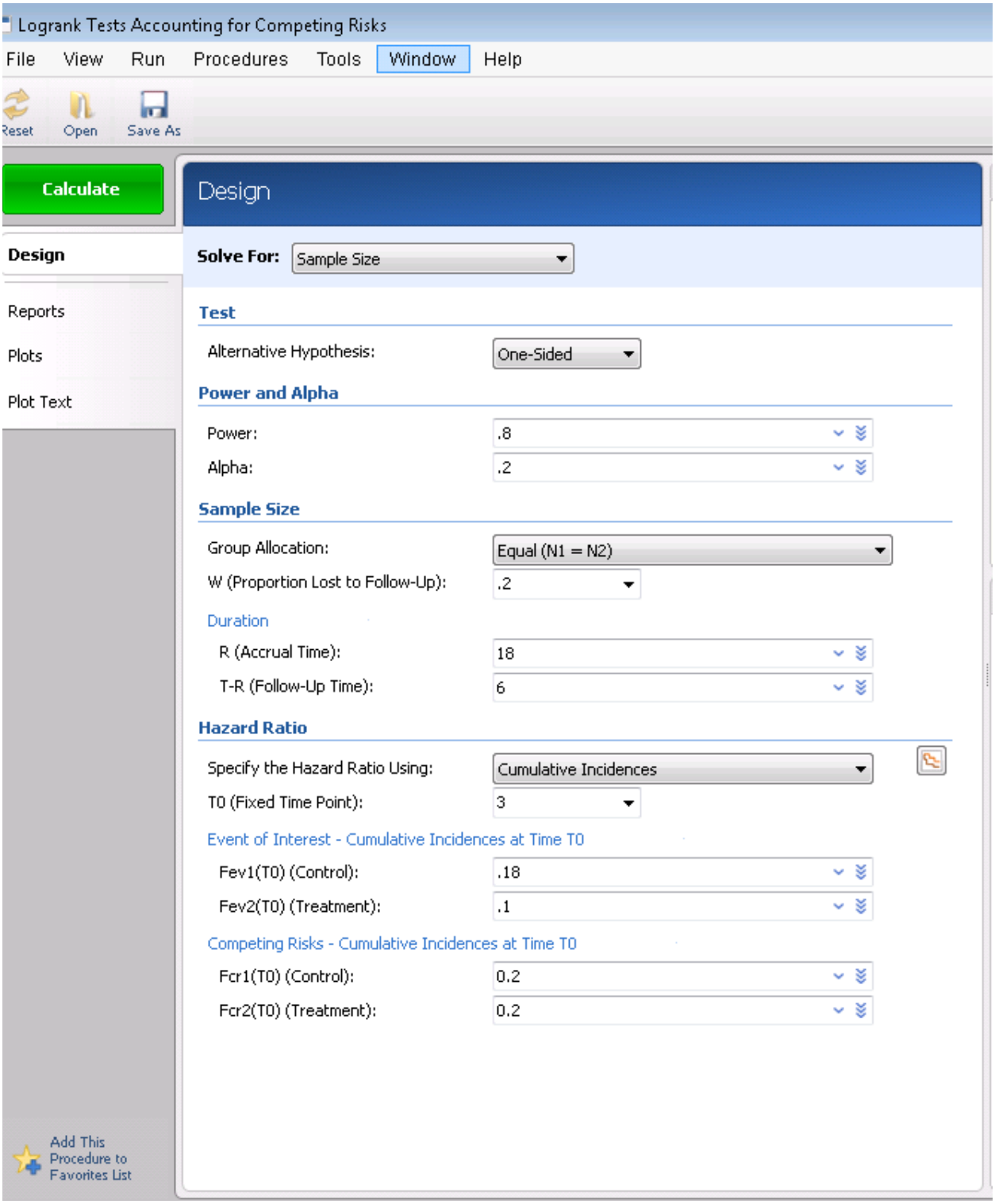
Report Definitions

T0 is the base time at which the cumulative incidences are calculated.
W is the proportion of the individuals lost to follow-up during the entire study.
Power is the probability of rejecting a false null hypothesis. Power should be close to one.
N is the total sample size of both groups combined.
N1 and N2 are the sample sizes for the control and treatment groups, respectively.
p1 is the proportion of the total sample size (N) that is assigned to the control group.
HR is the hazard ratio (hev2/hev1), the treatment group's hazard rate divided by the control group's hazard rate for the event of interest.
Fev1 and Fev2 are the cumulative incidences at time T0 for the event of interest in the control and treatment groups, respectively.
Fcr1 and Fcr2 are the cumulative incidences at time T0 for the competing risk factors in the control and treatment groups, respectively.
R is the accrual or entry time for the study.
T-R is the follow-up time for the study. T is the total time.
Alpha is the probability of rejecting a true null hypothesis. It should be small.
Beta is the probability of accepting a false null hypothesis. It should be small.
E is the total number of events required for the study.
E1 and E2 are the number of events required for the control and treatment groups, respectively.
Pr(ev) is the overall probability of observing the event of interest during the study.
Pr(ev1) and Pr(ev2) are the probability of observing the event of interest in a subject during the study for the control and treatment groups, respectively.
hev1 and hev2 are the hazard rates for the event of interest in the control and treatment groups, respectively.
hcr1 and hcr2 are the hazard rates for the competing risk factors in the control and treatment groups, respectively.
Rpt Row is a line number assigned to allow corresponding report lines to be identified.

Logrank Tests Accounting for Competing Risks

Summary Statements

When accounting for competing risks, a one-sided logrank test with an overall sample size of 102 subjects (51 in the control group and 51 in the treatment group) achieves 80.195% power at a 0.200 significance level to detect a hazard ratio of 0.5251. The study lasts for 24 time periods with an accrual (entry) time of 18 periods and a follow-up time of 6 periods. The cumulative incidence proportions at time 3 for the event of interest are 0.1800 in the control group and 0.1000 in the treatment group. The cumulative incidence proportions at time 3 for the competing risk factors are 0.2000 in the control group and 0.2000 in the treatment group. The proportion of subjects lost to follow-up during the entire study is 0.2.


Logrank Tests Accounting for Competing Risks
File View Run Procedures Tools Window Help
Reset Open Save As
Calculate
Design
Design
Reports
Plots
Plot Text
Solve For: Sample Size
Test
Alternative Hypothesis: One-Sided
Power and Alpha
Power: .8
Alpha: .2
Sample Size
Group Allocation: Equal (N1 = N2)
W (Proportion Lost to Follow-Up): .2
Duration
R (Accrual Time): 18
T-R (Follow-Up Time): 6
Hazard Ratio
Specify the Hazard Ratio Using: Cumulative Incidences
T0 (Fixed Time Point): 3
Event of Interest - Cumulative Incidences at Time T0
Fev1(T0) (Control): .18
Fev2(T0) (Treatment): .1
Competing Risks - Cumulative Incidences at Time T0
Fcr1(T0) (Control): 0.2
Fcr2(T0) (Treatment): 0.2
Add This Procedure to Favorites List

Conditional Power Analysis of Two Proportions

Numeric Results for Conditional Power of the Two Proportion Test
Null Hypothesis: P1 = P2 Alternative Hypothesis: P1 > P2

Cond. Power	Pred. Power	Total Sample Size N1|N2	Current Sample Size n1k|n2k	Prop. Group 1 P1	Prop. Group 2 P2	Test Statistic Zk	Alpha	Futility
0.03451	0.00172	51|51	25|25	0.2	0.1	1.500	0.20000	0.96549
0.02766	0.00108	51|51	25|25	0.2	0.1	1.600	0.20000	0.97234
0.02198	0.00067	51|51	25|25	0.2	0.1	1.700	0.20000	0.97802
0.01732	0.00041	51|51	25|25	0.2	0.1	1.800	0.20000	0.98268
0.01353	0.00024	51|51	25|25	0.2	0.1	1.900	0.20000	0.98647
0.01048	0.00014	51|51	25|25	0.2	0.1	2.000	0.20000	0.98952

References

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Proschan, M., Lan, K.K.G., Wittes, J.T. 2006. Statistical Monitoring of Clinical Trials. Springer. New York.
Chang, Mark. 2008. Classical and Adaptive Clinical Trial Designs. John Wiley & Sons. Hoboken, New Jersey.

Report Definitions

Conditional Power is the probability of rejecting a false null hypothesis at the end of the study given the data that have emerged so far.
Predicted Power is the average conditional power, averaged over the effect size.
N1|N2 are the anticipated total sample sizes of groups 1 and 2.
n1k|n2k are the sample sizes of groups 1 and 2 obtained through stage k.
P1 is the response proportion for groups 1 and 2 under the null hypothesis.
P2 is the response proportion for group 2 under the alternative hypothesis.
Zk is the value of the test statistic from the observed data at stage k.
Alpha is the probability of rejecting a true null hypothesis.
Futility is one minus the conditional power. A value greater than 0.9 or 0.8 indicates the study should be stopped because there is little chance of achieving statistical significance.

Summary Statements

The first 25 of 51 subjects in group 1 and 25 of 51 subjects in group 2 achieve 3% conditional power to detect a difference of -0.1 at a significance level of 0.20000 using a one-sided test. The value of the proportion in group 1 under the alternative hypothesis is 0.2. The value of the proportion in group 2 under the alternative hypothesis is 0.1. The value of the test statistic, Zk, from data that have emerged through look k is 1.500. The futility index is 0.96549.

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Appendix A – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

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

Zip code: ___ ___ ___ ___ ___

Sex: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic
☐Non-Hispanic

Race (choose all that apply): ☐ White ☐Black ☐ Asian
☐ Pacific Islander ☐ Native American

Marital status: ☐ Single ☐ Married/Domestic partner
☐ Separated/Divorced ☐ Widowed

Primary Diagnosis: _____

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

Education: ☐ High school or less ☐Some college ☐ College Graduate
☐ Graduate School ☐ Doctorate

Health Insurance: ☐ Private plan ☐ Medicare ☐ Medicaid ☐ Military ☐ None

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: ___ ___ / ___ ___ / ___ ___

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

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

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix B – Subject Eligibility Checklist

Inclusion Criteria (as outlined in study protocol)	Criteria is met	Criteria is NOT met	Source Used to Confirm * (Please document dates and lab results)
Diagnosis of cancer, not including multiple myeloma or lymphoma/leukemia.			
Radiographic evidence* of bone metastases within 8 weeks of study for non-weight bearing sites and 4 weeks for weight bearing sites. The patient must have pain which appears to be related to the radiographically documented metastasis in the opinion of the treating physician, and the decision has been made by the responsible clinician that a course of palliative external beam radiation therapy is appropriate treatment. Multiple sites eligible if they can be included in no greater than 3 treatment sites and not all identifiable lesions will require treatment unless they are painful lesions. *This should be one of the following: Plain Film, Bone Scan, PET scan, CT scan, or MRI.	☐	☐	
The involved bone(s) is/are orthopedically stable and not in need of stabilization via either definitive RT, surgical intervention, or both.	☐	☐	
Eligible Treatment Sites Are: Weight bearing sites: 1. pelvis (excluding pubis) 2. femur 3. sacrum and/or sacroiliac joints 4. tibia 5. up to 5 consecutive cervical, thoracic or lumbar vertebral bodies 6. lumbosacral spine Non-weight bearing sites: 5. up to 5 consecutive cervical, thoracic or lumbar vertebral bodies 6. lumbosacral spine 7. up to 3 consecutive ribs 8. humerus 9. fibula 10. radius ± ulna 11. clavicle 12. sternum 13. scapula 14. pubis 15. skull 16. bones of hands or feet If multiple sites are treated, the treatment site is included as weight-bearing if any of the sites include the pelvis, sacrum, femur or tibia.	☐	☐	

Pain score of at least 5 on a scale of 0 – 10 within a week of enrollment OR pain score < 5 with ≥ 60 mg of morphine (or equivalent) per day.	☐	☐	
ECOG performance status of 0-3.	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document.	☐	☐	
Negative pregnancy test at study registration.	☐	☐	
Life expectancy of at least 12 weeks as deemed by the treating oncologist.	☐	☐	
Patients will be eligible for treatment of multiple synchronous osseous sites only if those sites can be included in no more than three treatment sites. For patients with painful metastases that are contiguous but do not fit into the definition of a site listed above, those patients will still be eligible but will be considered to have two treatment sites. For example, a patient with a lesion of T4, T7 and T9 would be eligible but would be considered as two treatment sites since more than five consecutive vertebral bodies would be treated. These lesions could be treated with one field, even though the treatment is coded as two sites.	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Previous radiotherapy or palliative surgery to the painful site that is planned for treatment.	☐	☐	
Spinal cord or cauda equine compression/effacement in vertebral metastases with neurologic symptoms other than pain for the lesion that is planned for treatment.	☐	☐	

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

ORIS Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Treating Physician**: _____ 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 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

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 should be 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.

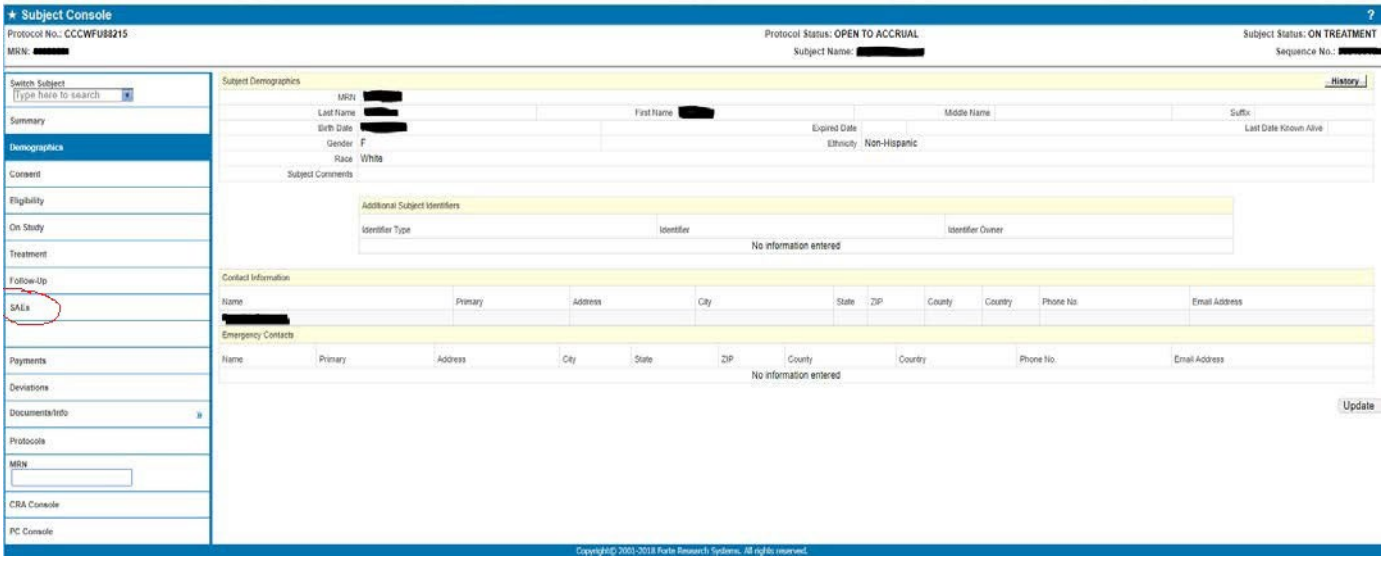
Acronyms

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

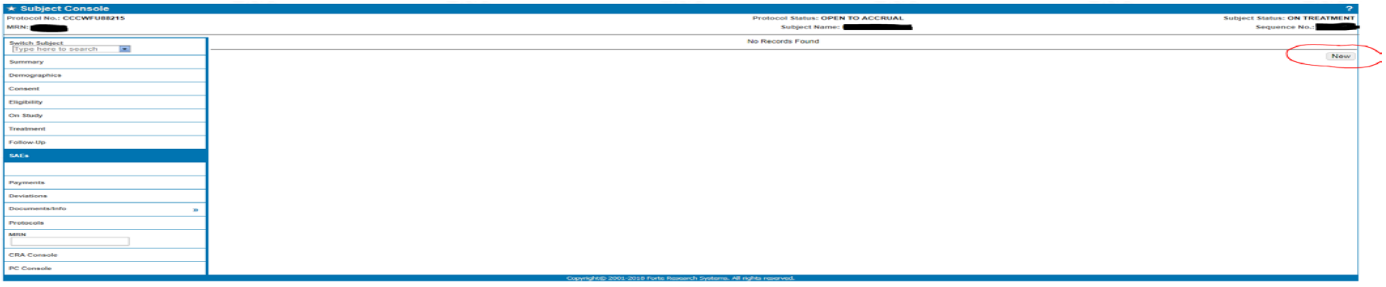
Screen Shots:

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

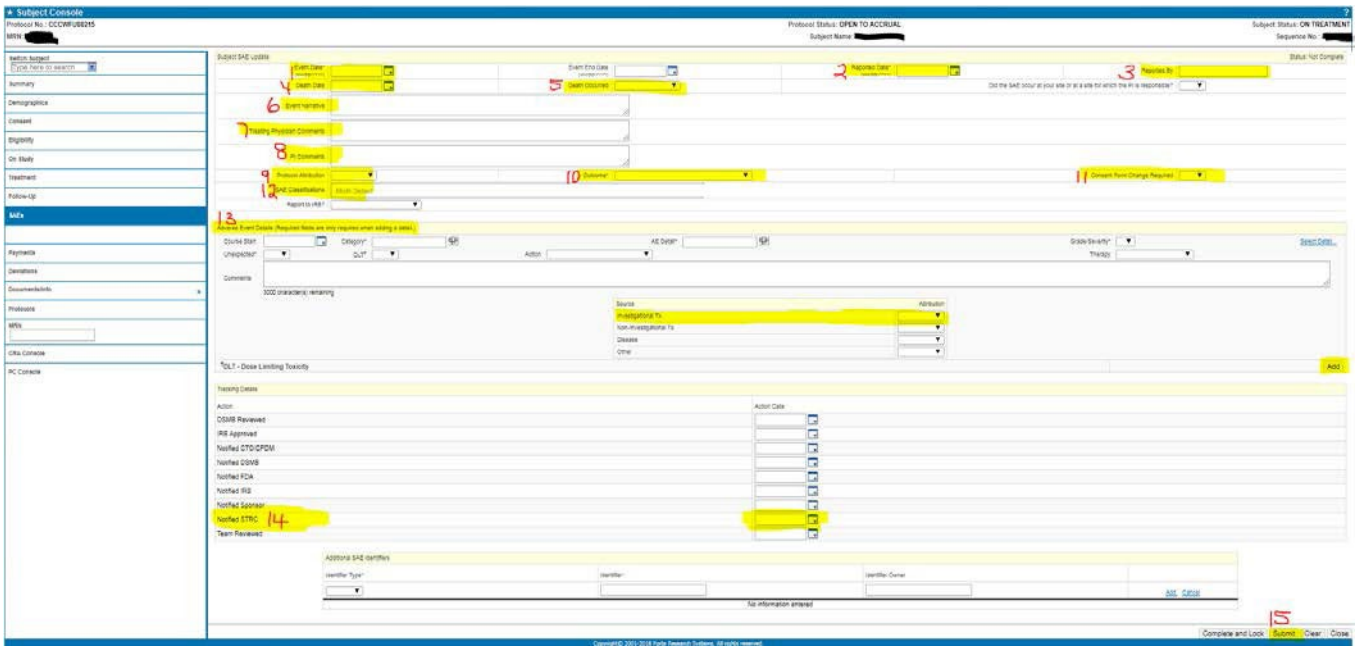
Screen Shot 1:



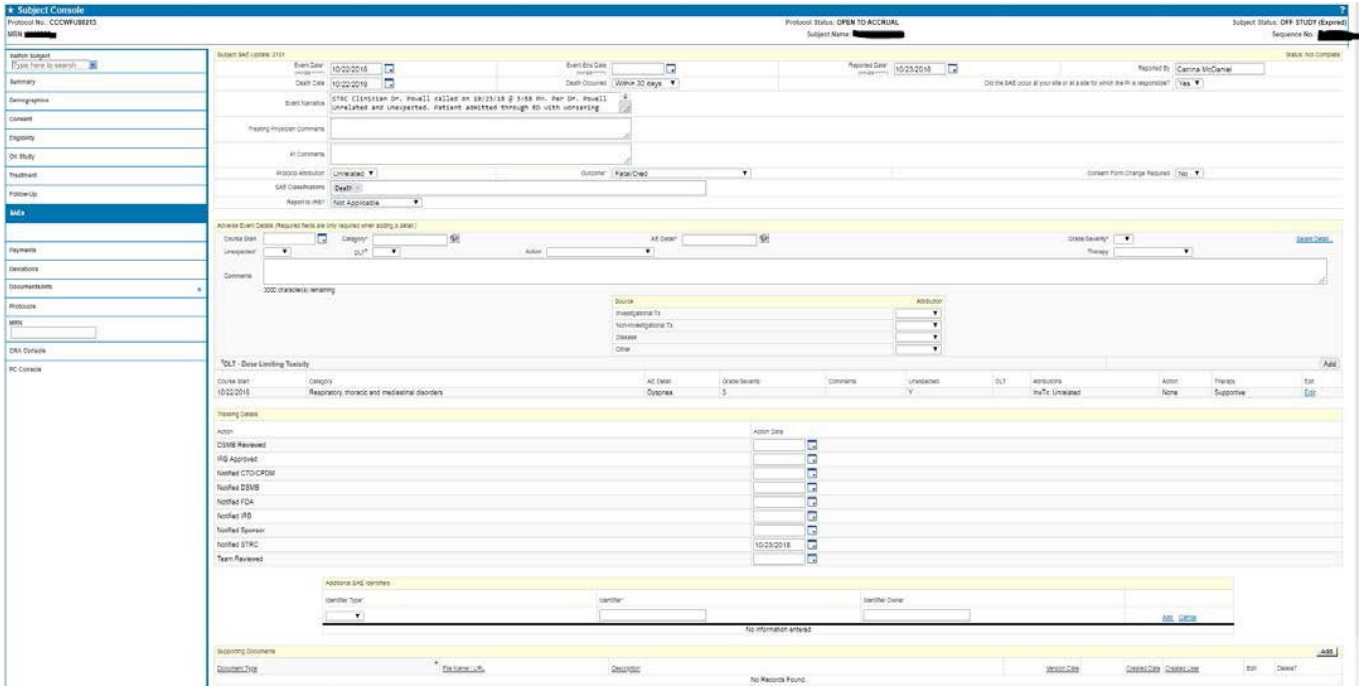
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix E – Baseline Data Collection Form

1. Medical history (check all that apply):
   - ☐ Myocardial infarction
   - ☐ Congestive heart failure
   - ☐ Peripheral vascular disease
   - ☐ Cerebrovascular disease
   - ☐ Dementia
   - ☐ Chronic pulmonary disease
   - ☐ Connective tissue disease
   - ☐ Peptic ulcer disease
   - ☐ Liver disease – ☐ mild ☐ moderate ☐ severe
   - ☐ Diabetes – end organ damage? Yes ☐ No ☐
   - ☐ Hemiplegia
   - ☐ Other cancer – specify _____
   - ☐ AIDs
   - ☐ Other medical condition – specify _____

   Other sites of metastases: Yes ☐ No ☐ N/A ☐
   If yes:
   a. Brain: Yes ☐ No ☐
   b. Liver: Yes ☐ No ☐
   c. Other: _____

2. Medications (including pain meds):

Concurrent medications:

a. Name:_____ Dose:_____ Frequency:_____ Date started:_____
b. Name:_____ Dose:_____ Frequency:_____ Date started:_____
c. Name:_____ Dose:_____ Frequency:_____ Date started:_____
d. Name:_____ Dose:_____ Frequency:_____ Date started:_____
e. Name:_____ Dose:_____ Frequency:_____ Date started:_____
f. Name:_____ Dose:_____ Frequency:_____ Date started:_____

Currently using bisphosphonates/Denosumab? Yes ☐ No ☐

If yes:

Name:_____ Dose:_____ Frequency:_____ Started:_____Prior Cancer Therapy:

a. Name:_____ Treatment Regimen:_____
b. Name:_____ Treatment Regimen:_____
c. Name:_____ Treatment Regimen:_____

Change in systemic chemotherapy in past 4 weeks? Yes ☐ No ☐ N/A ☐

Change in hormonal therapy in past 4 weeks? Yes ☐ No ☐ N/A ☐

Change in use of bisphosphonates in past 4 weeks? Yes ☐ No ☐ N/A ☐

Change in immunotherapy in past 4 weeks? Yes ☐ No ☐ N/A ☐

3. Performance Status (check one):

ECOG PERFORMANCE STATUS	
GRADE	**Description**
☐ **0**	Fully active, able to carry on all pre-disease performance without restriction
☐ **1**	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
☐ **2**	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
☐ **3**	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
☐ **4**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
☐ **5**	Dead

4. Nutrition status:
   a. Height: _____
   b. Weight: _____
   c. BMI (kg/M^2)_____
   d. History of weight loss: (within the last three months prior to enrollment) Yes ☐ No ☐
      If yes, date of weight loss:__/__/__
      If yes, amount of weight loss: ____
5. Vital signs:
   a. HR_____
   b. BP___/___
   c. RR____
   d. Temp (^{o}F)____

6. Physical Exam

Derm – ☐ WNL ☐ Abnormal, specify _____
HEENT – ☐ WNL ☐ Abnormal, specify _____
CV – ☐ WNL ☐ Abnormal, specify _____
Pulm – ☐ WNL ☐ Abnormal, specify _____
GI – ☐ WNL ☐ Abnormal, specify _____
Other – ☐ Abnormal, specify _____

7. Documentation of negative pregnancy test for women of child-bearing potential?

Yes ☐ No ☐, reason_ _____ Not applicable☐

Appendix F – Treatment Data Collection Form

Time point of assessment:

☐ Treatment administration Tx #1 ☐ Tx #2 ☐

☐ 3 months post treatment
☐ 6 months post treatment

1. Nutrition status:
   - **a.** Weight: _____
   - **b.** BMI (kg/M^2)_____
   - **c.** History of weight loss: (since last assessment) Yes ☐ No ☐
     If yes, date of weight loss:__/__/__
     If yes, amount of weight loss: ____
2. Vital signs:
   a. HR_____
   b. BP___/___
   c. RR____
   d. Temp (°F)___

Appendix G – Patient Questionnaire

Time point of assessment:

☐ Baseline
☐ 3 months post treatment
☐ 6 months post treatment

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
2. Do you need to stay in bed or a chair during the day?	1	2	3	4
3. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
4. Were you short of breath?	1	2	3	4
5. Have you had pain?	1	2	3	4
6. Have you had trouble sleeping?	1	2	3	4
7. Have you felt weak?	1	2	3	4
8. Have you lacked appetite?	1	2	3	4
9. Have you felt nauseated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
10. Have you been constipated?	1	2	3	4
11. Were you tired?	1	2	3	4
12. Did pain interfere with your daily activities?	1	2	3	4
13. Did you feel tense?	1	2	3	4
14. Did you feel depressed?	1	2	3	4

For the following question please circle the number between 1 and 7 that best applies to you

15. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

We are interested in knowing about the stresses you are experiencing with your treatment. Please answer each question regarding how you have perceived stress in the past week on a scale from 1 = "Never" to 5 = "Very Often".

	Never	Almost Never	Sometimes	Fairly Often	Very Often
In the last month, how often have you been upset because of something that happened unexpectedly?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you felt that you were unable to control the important things in your life?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you felt nervous and "stressed"?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you felt confident about your ability to handle your personal problems?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you felt that things were going your way?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you found that you could not cope with all the things that you had to do?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you been able to control irritations in your life?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you felt that you were on top of things?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you been angered because of things that were outside your control?	**1**	**2**	**3**	**4**	**5**
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	**1**	**2**	**3**	**4**	**5**

We are interested in knowing about your support network. Please read the statements and answer how true or false each is for you. The answers range from 1= "Definitely False for you" to 4 = "Definitely True for you".

	Definitely false for you	Probably false for you	Probably true for you	Definitely true for you
If you wanted to go on a trip for a day (for example, the country or mountains), you would have a hard time finding someone to go with you. Would you say this is…	**1**	**2**	**3**	**4**
You feel that there is no one you can share your most private words and here's what. Would you say this is…	**1**	**2**	**3**	**4**
If you were sick, you could easily find someone to help you with your daily chores. Would you say this is…	**1**	**2**	**3**	**4**
There is someone you can turn to for advice about handling problems with your family.	**1**	**2**	**3**	**4**
If you decide one afternoon that you would like to go to a movie that evening, you can easily find someone to go with you.	**1**	**2**	**3**	**4**
When you need suggestions on how to deal with a personal problem, you know whoyou can turn to.	**1**	**2**	**3**	**4**
You don't often get invited to do things with others.	**1**	**2**	**3**	**4**
If you had to go out of town for a few weeks it would be difficult to find someone who would look after your house or apartment (the plants, pets, garden, etc.).	**1**	**2**	**3**	**4**
And if you wanted to have lunch with someone, you could easily find someone to join you.	**1**	**2**	**3**	**4**
If you were stranded 10 miles from home, there is someone you could call who would come and get you.	**1**	**2**	**3**	**4**
If a family crisis arose, it will be difficult to find someone who could give you good advice about how to handle it.	**1**	**2**	**3**	**4**
If you needed some help in moving to a new house or apartment, you would have a hard time finding someone to help you.	**1**	**2**	**3**	**4**

CCCWFU # 01416 Patient ID:_____ Date of completion: _____

We are interested in knowing about the satisfaction you are experiencing with your treatment. Please answer each question regarding your satisfaction with your treatment in the past week on a scale from 1 = "Strongly Agree" to 5 = "Strongly Disagree".

	Strongly Agree	Agree	Neither	Disagree	Strongly Disagree
I felt that my health concerns were understood.	**1**	**2**	**3**	**4**	**5**
I felt that I was treated with courtesy and respect.	**1**	**2**	**3**	**4**	**5**
I felt included in decisions about my health.	**1**	**2**	**3**	**4**	**5**
I was told how to take care of myself.	**1**	**2**	**3**	**4**	**5**
I felt encouraged to talk about my personal health concerns.	**1**	**2**	**3**	**4**	**5**
I felt I had enough time with my doctor.	**1**	**2**	**3**	**4**	**5**
My questions were answered to my satisfaction.	**1**	**2**	**3**	**4**	**5**
Making an appointment was easy.	**1**	**2**	**3**	**4**	**5**
I knew what the next step in my care would be.	**1**	**2**	**3**	**4**	**5**
I feel confident in how I deal with the health care system.	**1**	**2**	**3**	**4**	**5**
I was able to get the advice I needed about my health issues.	**1**	**2**	**3**	**4**	**5**
I knew who to contact when I had a question.	**1**	**2**	**3**	**4**	**5**
I received all the services I needed.	**1**	**2**	**3**	**4**	**5**
I am satisfied with the care I received.	**1**	**2**	**3**	**4**	**5**
The doctors seemed to communicate well about my care.	**1**	**2**	**3**	**4**	**5**
I received high quality care from my regular doctor.	**1**	**2**	**3**	**4**	**5**
I received high quality care from my specialists.	**1**	**2**	**3**	**4**	**5**
My regular doctor was informed about the results of the tests I got.	**1**	**2**	**3**	**4**	**5**

Appendix H – Numerical Rating Pain Scale (NRPS)

Time point of assessment:

☐ Screening/Baseline

☐ 1-month post treatment
☐ 2-months post treatment
☐ 3 months post treatment
☐ 6 months post treatment

Please rate your pain by circling the one number that best describes your pain at its WORST in the past 3 days.

0 1 2 3 4 5 6 7 8 9 10
No Pain Worst possible pain

Site of Pain: _____

Toxicity Evaluation:

Did the patient report any adverse events or toxicities? **Y** / **N** / **N/A**

If Yes, Describe and add to AE Log:

_____
_____
_____
_____
_____
_____
_____

Any changes to the patient's medications? **Y** / **N** / **N/A**

If yes, Name:_____ Dose:_____ Frequency:_____ Date started:_____

Name:_____ Dose:_____ Frequency:_____ Date started:_____

Name:_____ Dose:_____ Frequency:_____ Date started:_____

Name:_____ Dose:_____ Frequency:_____ Date started:_____

Appendix I – CCCWFU 01416 Adverse Event (AE) Log

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

Start Date: _____ **End Date: _____** **Time Point (choose one)** 1 month

Adverse Event CTC Term	**Value** (-5 if nonnumeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	**Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxitity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** (1-IRB 2-STRC, 3-FDA 4-Sponsor)
Nausea							1				
Vomiting							1				
Diarrhea							1				
Skin erythema							1				
alopecia							1				
esophagitis							1				
myelosuppression							1				
Urinary urgency							1				
Urinary frequency							1				
pneumonitis							1				
Pain (increased from baseline)											

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

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix I – CCCWFU 01416 Adverse Event (AE) Log

PID: _____ **MRN: _____**

PI: _____

Start Date: _____ **End Date: _____** **Time point (choose one):** 2 months 3 months 6 months

OTHER Adverse Events	Value (-5 if non-numeric)	Grade(0-5) per CTC	Start Date	Attribution 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	Treating MD Initials/Date	End Date	Expected 1=Yes 0=No	Serious Adverse Event (SAE) 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** (1-IRB 2-STRC, 3-FDA 4-Sponsor)
Fistula formation										
Bowel obstruction										
Bowel perforation										
Fracture of the bone										
Damage to spinal cord (myelitis)										

Appendix J – Re-Treatment Data Form

1) Did re-treatment occur? Yes ☐ No ☐

   a. If yes, when was the first re-treatment? __/___/___

Appendix K – Post-Treatment Imaging

DATA COLLECTION FORM

PID: ___ ___ ___ ___ ___ ___ ___ ___ **Date Completed:** ___ ___ / ___ ___ / ___ ___

PI: Doris Brown, M.D.

Study Number: CCCWFU 01416

To be completed by study staff:

	To be completed by study staff:	
Time Point	Type of Imaging (CT, X-ray, etc.)[b]	Date of Imaging[b]
3 Months[a]		
6 Months[a]		

To be completed by the investigators (Dr. Willey):

	Cortical Bone Thickness (mm)[b]	Bone Mineral Density (mg HA/cc)[b]
3 Months[a]		
6 Months[a]		

[a]10-18 weeks from final treatment date (3-month) and 20-34 weeks from final treatment date (6-month visit).
[b]NA if none