UNIVERSITY OF SOUTHERN CALIFORNIA/KENNETH NORRIS, JR. COMPREHENSIVE CANCER CENTER AND HOSPITAL

16M-18-2

Phase II Multi-Institutional Study of Low-Dose (2Gy x 2) Palliative Radiotherapy in the Treatment of Symptomatic Bone metastases from Multiple Myeloma

Principal Investigator:

Leslie Ballas, MD
USC Keck School of Medicine
1441 Eastlake Ave
NOR G350
Los Angeles, CA 90033
323-865-3050
323-865-0000
LBallas@med.usc.edu

Co-Investigator(s):

Ann Mohrbacher, MD
Division of Hematology

Kevin Kelly, MD
Division of Hematology

Adam Garsa, MD
Department of Radiation Oncology

Richard Jennelle, MD
Department of Radiation Oncology

For off-site Co-PI include:
Richard Bakst, MD
Mt. Sinai School of Medicine
1184 Fifth Ave
New York, NY
212-241-3545
Richard.bakst@mtsinai.org

Ima Paydar, MD
University of Pennsylvania
3400 Civic Center Blvd, PCAM 4W
Philadelphia, PA
215-615-5858
Ima.Paydar@pennmedicine.upenn.edu

Andrea Ng, MD
Dana Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
617-632-3400
Andrea_Ng@dfci.harvard.edu

UNIVERSITY OF SOUTHERN CALIFORNIA/KENNETH NORRIS, JR. COMPREHENSIVE CANCER CENTER AND HOSPITAL

Mohammad Khan, MD
Emory University
1365 Clifron Rd NE, office A1312
Atlanta, GA
404-778-3473
m.k.khan@emory.edu

Chirayu Patel, MD, MPH
Massachusetts General Hospital
100 Blossom Street
Boston, MA 02114
617-726-9627
cpatel@mgh.harvard.edu

Joanna Yang, MD, MPH
University of California San Francisco
Box 1708, 1600 Divisadero St, H1031
San Francisco, CA 94115
415-353-9894
Joanna.Yang@ucsf.edu

Parag Sanghavi, MD
UC San Diego Health
3855 Health Sciences Drive
La Jolla, CA 92093
psanghvi@health.ucsd.edu

Biostatistician: Joshua Millstein
USC Keck School of Medicine
NTT 4419A
(323) 865-0414 / (323) 361-8582
joshua.millstien@usc.edu

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Research Office: **CLINICAL INVESTIGATIONS SUPPORT OFFICE (CISO)**
1441 Eastlake Avenue, Room 7310E
Los Angeles, California 90089-9177
Telephone (323) 865-0451
Email: ciso.clinical@med.usc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:

PI Signature:

Institutional Name:

Date:

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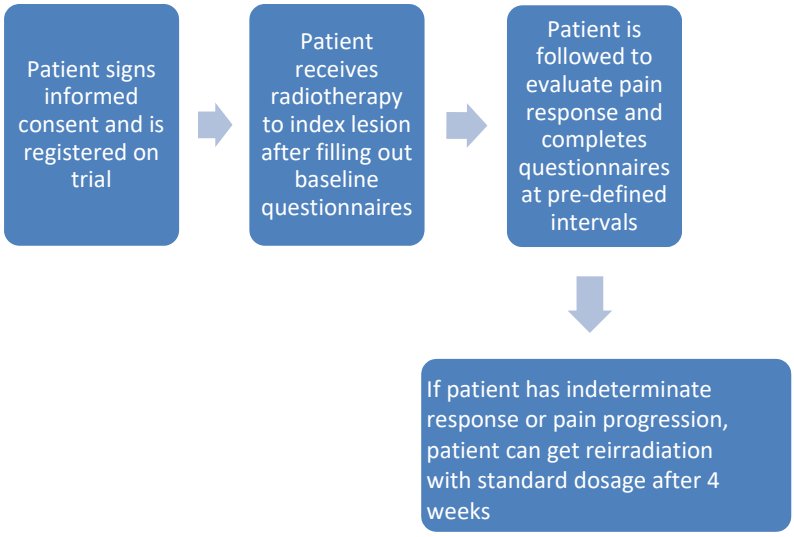
LIST OF ABBREVIATIONS

RT	Radiotherapy
MM	Multiple Myeloma
CR	Complete response
PR	Partial response
PP	Pain progression
IR	Indeterminate response
RTOG	Radiation Therapy Oncology Group
BPI	Brief Pain Index
EORTC QLQ-BM22	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases Module
EORTC QLQ-C20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire
IMWG	International Myeloma Working Group
ISS	International Staging System
QOL	Quality of Life
OAR	Organs at Risk
GTV	Gross Tumor Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
3DCRT	3-Dimensional Conformal Radiotherapy
IMRT	Intensity Modulated Radiotherapy
PE	Physical Exam
CTCAE	Common Terminology Criteria for Adverse Events
AE	Adverse Event

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II Multi-Institutional Study of Low-Dose (2Gy x 2) Palliative Radiotherapy in the Treatment of Symptomatic Bone metastases from Multiple Myeloma
Short Title	Low-dose RT for myeloma palliation
Protocol Number	16M-18-2
Phase	Phase II
Methodology	Prospective multi-institution
Study Duration	2 years
Study Center(s)	Multi-institution with predicted 6 sites
Objectives	To determine if 2Gy x 2 provides patient-reported pain relief and/or decrease in analgesia use in patients with painful bone lesions from multiple myeloma at 4 weeks.
Number of Subjects	100
Diagnosis and Main Inclusion Criteria	Patients must have a multiple myeloma diagnosis with a painful bone lesion that can be visualized on imaging (CT/XRay/MRI/PET) and that is not causing spinal cord compression or structural instability/fracture
Study Product(s), Dose, Route, Regimen	Radiotherapy given at 2Gy/fraction for 2 days
Duration of administration	2 days
Reference therapy	Standard radiation dosing is typically 20-24 Gy in 10-12 treatments
Statistical Methodology	Two-stage Phase II design

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Osteolytic bone lesions are detected at diagnosis in 70-80% of patients with multiple myeloma (MM)[1]. Bone lesions from MM often cause pain. Radiotherapy is effective in providing pain relief from bone metastases with some degree of pain relief in approximately 90% of patients[2-7]. There is no consensus as to the most effective dose or fractionation for palliation, however lower doses of RT are used in palliation of MM (compared with solid tumor bone metastases) because it a very radiosensitive tumor[8,9]. In the era of excellent systemic therapies, patients with MM are living longer[10], and palliative RT is not only still an important part of the treatment paradigm in these patients but also may be required to additional sites over time.

1.2 Rationale

Rationale for palliative RT in osseous metastases

Radiation Therapy Oncology Group (RTOG) 74-02 was an early multicenter trial comparing different doses of radiation therapy in the palliation of bone metastases[11].This study enrolled patients with varying histologies either with a single osseous metastasis or multiple osseous metastases. Treatment doses ranged from 1500cGy to 4050cGy treated in 300-500cGy fractions. 90% of patients experienced some degree of pain relief with no significant difference in dose or fractionation schedules in terms of time to pain relief, duration of pain relief or proportion of patients with pain relapse[11]. Patients who were treated with the lowest doses did have higher rates of retreatment (the study allowed for re-treatment of the same site if there was not complete pain relief) upon secondary analysis[12]. This study did not incorporate patient reported outcomes and physicians did all pain reporting.

Since this initial trial comparing fractionation schedules for palliative radiotherapy, many studies have randomized patients to short-course (<=5 fractions) vs long-course (>5 fractions) palliative treatment. RTOG 9714 randomized breast and prostate cancer patients to 8Gy single treatment vs 30Gy in 10 fractions and found that both regimens were equivalent in terms of pain and narcotic relief at 3 months[13]. There was again higher retreatment in the 8 Gy arm but more acute toxicity in the 30Gy arm. Interestingly, their CR rate was only 16%, which was lower than the 54% of patients who had CR on RTOG 7402. Of course, the authors point out that in 9714, patient reported outcomes were collected – and a rigorous pain evaluation tool was used (the Brief Pain Index, BPI) compared to the physician reported pain outcomes and 4-point pain scale used in 7402. In subset analysis of this trial specifically looking at painful vertebral body metastases, the results were similar: no statistically different pain or narcotic relief in the 8Gy vs 30Gy arms at 3 months, more retreatment in the single fraction arm and less acute toxicity in the single fraction arm[14]. Authors proposed that pain response was not solely dependent on decreasing tumor burden but also effects on normal tissues. Based on the work of Hoskin, et al, the authors suggest the effectiveness of radiation is associated with the RT effect on osteoclasts and the RANK (receptor activator of nuclear factor κB) signaling pathway[13].

A systematic review of palliative radiotherapy for bone metastases showed that there was no difference in overall response rates for pain or complete response rates for pain between single fraction schedules and multiple fraction schedules[15].

Despite multiple trials that show equivalence in pain control between shorter fraction and longer-fraction palliation, physicians still use varying treatment schedules to palliate bone pain in the setting of solid tumors. Chow, *et al*. also examined patterns of practice surveys that have been done around the world and found that there was a clear reluctance to use single fraction treatment[15].

Multiple Myeloma is different from solid tumors

Most of the trials that evaluate pain control in the treatment of bone metastases, contain very few multiple myeloma patients or exclude them because it is inherently a different disease with different ability to respond to RT. Systemic therapies in MM treatment have improved over the last decade leading to longer patient survival[16,17]. Early work defining the radio-responsiveness of human tumors and the cell survival of tumor cells exposed to radiotherapy grouped tumors according to their clinical radio-responsiveness. Multiple myeloma, lymphoma and neuroblastoma were the most sensitive tumors to radiotherapy[9,18]. Clonogenic myeloma cells, when radiated in vitro, had a more effective reduction when higher dose-rates and single doses were used compared to the same total dose administered in multiple fractions[8]. Normal bone marrow, however, has a higher surviving fraction of cells when exposed to fractionated RT compared with single fraction treatment – although it did not reach statistical significance[8].

Initial trials of the use of radiotherapy in the management of multiple myeloma from the Mallinckrodt Institute of Radiation Oncology found that because myeloma of the bone is relatively sensitive to radiation, pain relief could be seen at 10-15Gy even though the dose most commonly prescribed was 15-20Gy. This corroborated the findings of Norin, who, in 1957, published that most cases of multiple myeloma, pain relief could be achieved with 10Gy[19]. 13 patients were treated with 0-10Gy (without mention of fractionation) by Leigh, et al. as part of a larger myeloma study, and they were found to have over 90% pain relief, 15% of which had a PR. This was not dissimilar to the findings of the 30 patients who received >30Gy[20]. The benefit to lower doses is that it minimizes associated bone marrow suppression allowing for maximal chemotherapy delivery[7]. One caveat to the radiotherapy delivered during this era did not have the benefits of modern imaging or radiation treatment planning.

RT in palliation of MM

Because multiple myeloma patients have multiple bone lesions and live for an extended period of time with bone lesions, many patients have more than one course of palliative RT for bone pain. Modern studies evaluating efficacy of radiotherapy in pain relief from bone metastases in multiple myeloma have reported pain relief in over 85% of patients[2-5] but these studies lacked rigor in reporting pain/outcomes. None of the retrospective single institution studies used similar methods to evaluate pain response; one used a numeric rating scale of 0-10, one a Likert scale evaluating analgesic use, and in two of the studies there was no mention of how pain relief was measured and was presumed to be subjectively collected at the time of follow-up. The dosing in the different reports varied within each study with most ranging from 8Gy to 40 Gy[2-5].

Balducci, *et al* did try to quantify the effect of RT by evaluating bone recalcification. Bone recalcification is an imperfect way to measure tumor response, however, the authors reported 50% had a radiologic response with a median follow-up of 57 months[3].

One study did randomize patients with multiple myeloma to 8Gy in 1 fraction or 30 Gy in 10 fractions, to compare pain relief, quality of life (QOL) and recalcification following different RT schedules. This study used the same general principles and doses as has been done in the setting of bone metastases from solid malignancies[6]. Pain was measured on a visual analog scale and a mean morphine-equivalent dose was calculated at 4, 12 and 24 weeks following RT. This study used the EORTC QLQ-C30 and QLQ-MY20 questionnaires to measure QOL. They found, like in other studies, that pain relief was seen in 80% of patients with no significant difference in analgesic response between the 8Gy and 30Gy groups. Pain relief was independent of concurrent chemotherapy. Recalcification was a significant factor predicating pain relief, but there was no significant difference in recalcification between groups. QOL improved in the 30Gy group ($p<0.05$) but not in a statistically significant way in the 8Gy group[6].

Despite multiple publications and even a randomized trial, there is no consensus on dose for palliation of painful bone metastases in multiple myeloma. The ILROG Guidelines for use of radiotherapy in plasma cell neoplasms suggested a range of acceptable doses: from hypofractionated 8Gy in 1 fraction to 20Gy in 5 fractions and conventional fractionation in the 20-30 Gy range[16]. Clearly, the issue of dose is still unsettled in this clinical setting.

Rationale for 2Gy x 2

Shorter courses of therapy are not only more convenient for patients and their families, but they also have less impact on timing of systemic therapies. There is precedent for using 2Gy x 2 in the palliation of lymphomas, which have similar radiosensitivity to myeloma[9]. Girinsky, *et al* used 2Gy x 2 fractions to treat refractory or relapsed low-grade lymphomas with a response rate of 81%[21,22]. The complete response rate was higher in extranodal sites compared to nodal sites and the 2-year freedom from progression rate in extranodal masses (19% of the study population) being 72%[21]. A larger study that followed that also evaluated 4Gy in the setting of recurrent indolent lymphoma showed a 92% response rate with a median time to local progression of 25 months without significant toxicity[23].

Pain and QOL questionnaires

Brief Pain Inventory (BPI)[24] will be used to assess severity, location, chronicity, degree of relief due to therapy, perceived availability of relief, depression and suffering. The 0-10 pain assessment from the BPI is the most highly correlated to enjoyment of daily activities, and has breakpoints that correlate with levels of interference[25]. The scale is 0-10, and there are breakpoints between scores of 4 and 5 and between 6 and 7, indicating that mild pain correlates with scores of 1-4, moderate pain with 5-6 and severe pain with scores of 7-10.

Reduction in pain from bone metastases is an important component to radiotherapy, but palliative treatment is also to maintain QOL. Tools have been developed to measure QOL in patients with bone metastases. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Bone Metastases Module (QLQ-BM22) is intended to assess how pain lowers QOL in patients with bone metastases[26]. This questionnaire has demonstrated that with decreased pain, patients have improvements in functional and psychosocial elements (physical as well as emotional)[26]. Furthermore, it has been validated to use in conjunction with the EORTC QLQ-C30, a general QOL tool for cancer patients[27].

International Consensus on Palliative Radiotherapy

Because clinical trials evaluating palliation of bone metastases have used varying endpoints, different pain scales, and varying eligibility criteria, the International Consensus on Palliative Radiotherapy created suggested endpoints for future clinical trials in bone metastases[28]. This group of 49 experts made formal recommendations for how to define pain response to treatment, the use of QOL questionnaires as well as pain scale measures, the use of systemic therapy and if it should be withheld around the time of RT, defined timing for re-irradiation, among other elements[28].

Based on their recommendations, all patients on this protocol will have their pain evaluated based on response categories that are self-reported. We also developed inclusion criteria for a minimum BPI score of >=5 or <5 with >=60 mg morphine requirement, patients cannot have prior RT to the index lesion, there must be radiographic evidence of a bone metastasis at the site of pain, patients will complete both a BPI and EORTC QLQ-BM22 to assess pain and QOL endpoints that are present within 3 days of completing the questionnaires, reirradiation will not be done in less than 4 weeks from completing the RT being evaluated on study, and changes in systemic therapy within the 4 weeks of RT are allowed, but will be recorded for analysis[28].

1.3 Correlative studies

The International Myeloma Working Group (IMWG) developed diagnostic, risk stratification and response criteria that has been proven to help prognostication for patients with MM. Abnormal cytogenetics are present in approximately 1/3 of patients with MM. The presence of t4;14, t(14;16), 17p13 deletion, 1p21 gain is associated with poor prognosis and the combination of monosomy and/or deletion of chromosome 13 by FISH, a Sβ2M level greater than 2.5 mg/l and an elevated plasma cell labeling index resulted in shorter survival[29,30]. Because both the Durie–Salmon Staging System and the International Staging System (ISS) are not useful for therapeutic risk stratification, the aforementioned prognostic markers provide a better estimate of differences in underlying myeloma biology.

For the purposes of this protocol, we plan to record information on cytogenetics, risk stratification and IMWG response criteria so as to see if the biology of the tumors stratifies patient's response to RT.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether treatment with 2Gy x 2 to a painful myeloma bone lesion achieves patient-reported pain reduction comparable to historical controls at 4 weeks.

2.2 Secondary Objectives

2.2.1 To assess QOL in patients treated with 2Gy x 2 to painful myeloma bone lesions.

2.2.2 To quantify analgesia use/reduction following 2Gy x 2 to a painful myeloma bone lesion. All opioid analgesia use will be converted into morphine equivalent in order to compare across the entire population.

2.2.3 To measure time to pain relief and duration of pain relief with 2Gy x 2.

2.3 Exploratory Objectives

To record cytogenetics and IMWG response criteria at diagnosis and prior to and following RT. Because these patients will be getting lab work regularly, we will only record previously obtained results and not require additional lab work. No patient will be ineligible if lab work is not available. We will be interested in recording the following information, when available, from the patient's record from diagnosis, before and after RT:

- FLC levels
- Serum and urine M-component
- Bone marrow plasma cell percentage
- Serum calcium
- Serum B2M
- Cytogenetics: t(4;14), t(14;16), 17p13, 1q21 gain, monosomy/deletion chromosome 13
- Plasma cell labeling index

To evaluate pain response at index lesion after the 2nd course of radiation (re-irradiation), if required.

2.4 Endpoints

2.4.1 Pain response

Pain will be measured using the BPI and QOL will be assessed with the EORTC QLQ-BM22 and EORTC QLQ-30 questionnaires. Questionnaires will be completed at baseline, 2, 4, 8 weeks and 6 months after completion of RT.

Pain response criteria have been developed by the International consensus on palliative radiotherapy. (see section 6.1)

3.0 PATIENT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

Patient may have more than one index lesion to be considered for the study treatment.

- All index lesion must be assessed separately and meet the eligibility criteria.
- BPI and EORTC QLQ-BM22 must be completed per index lesion.

3.1 Inclusion Criteria

3.1.1 Histologic diagnosis of Multiple Myeloma

3.1.2 Painful bone metastasis (index lesion) that has a radiographic correlate

3.1.3 Patient may have had any number of prior chemotherapy/immunotherapy regimens (changes to systemic therapy or use of bisphosphonates for 4 weeks before and after RT are allowed, but recording of these changes must be made so it can be accounted for)

3.1.4 Age ≥ 18 years.

3.1.5 ECOG 0-2

3.1.6 BPI score ≥2 (BPI for eligibility is the average from questions 3, 4, 5, and 6)

3.1.7 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Patients will be ineligible if the index lesion has received prior radiation therapy or prior palliative surgery. Patients may have received prior palliative or primary radiotherapy or surgery to other parts of the body, as long as the index lesion was not in the prior radiation fields and has not received prior palliative surgery.

3.2.2 Patients will also be ineligible if there is pathologic fracture or impending fracture at the site of the index lesion or planned surgical fixation of the bone at the index lesion.

3.2.3 Patients with clinical or radiographic evidence of spinal cord or cauda equina compression/effacement from the index lesion, and/or with index lesions located at the skull base or orbital lesions.

3.2.4 Patients must not be pregnant.

4.0 TREATMENT PLAN

4.1 Radiation Therapy

4.1.1 Treatment Planning

4.1.1.1 CT simulation: All patients will have a CT simulation for treatment planning. All tissues to be irradiated must be included in the CT scan. CT thickness will be 3mm or less. Use of IV contrast is at the discretion of the treating physician. Patient positioning and immobilization is left to the discretion of the treating physician but requires a reproducible setup that can be reproduced daily. A variety of immobilization devices may be utilized including a combifix, vacuum bag, alpha cradle, etc.

4.1.1.1.1 Risks associated with CT simulation and immobilization: none.

4.1.1.2 Target volumes

GTV, CTV and PTV will be based on the International Lymphoma Radiation Oncology Group Guidelines:

"Using the primary imaging of untreated lesions, the GTV should be outlined on the simulation study. Fusion of the primary imaging (PET/CT or MRI) with the simulation study can be helpful to define the GTV. Field placement practices based on anatomic landmarks are obsolete (e.g. fields to include one or two normal vertebral bodies above and below the grossly involved vertebra) and should not be used. In the palliative setting, it is reasonable to omit an additional margin from GTV to CTV as it is not critical to cover adjacent subclinical disease in the context of wider systemic disease. Whole bone coverage is generally not required[16]." The PTV should be expanded from the GTV/CTV to account for setup uncertainties during radiotherapy planning and treatment sessions and will vary by institution and immobilization used.

4.1.1.3 Normal Tissue Definitions

Normal tissues that constitute organs at risk (OAR) will vary depending on the location of the index lesion. Because of the low radiation dose used in this trial, no normal tissues are in danger of toxicity. Treating physicians should contour organs at risk at their discretion.

4.1.2 Technical Factors

4.1.2.1 Megavoltage equipment will be used with photon energy of ≥ 6MV. Treatment energy will be left at the discretion of the treating physician.

4.1.2.2 3DCRT should be used in almost all cases. If a physician needs to use IMRT, for some reason, then the prescribed dose should be delivered to ≥95% of the PTV.

4.1.3 Dose Fractionation

Patients will receive 2Gy each consecutive business day for 2 total treatments, or a total of 4Gy.

4.1.4 Re-treatment

Reirradiation at standard dosage should only be considered at ≥4 weeks following initial treatment for IR or PP. Patients who receive

re-irradiation will restart the follow up period: at 2 weeks, 4 weeks, 8 weeks and 6 months from the end of the second course of RT.

4.2 Toxicities

This dose of radiation should not produce any toxicities as radiotherapy side effects are related to dose. However, the treating physician should record toxicity, if seen, based on the location of treatment based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0) at the end of treatment and at all follow-up visits.

4.3 Concomitant Medications/Treatments

Patients can be on concurrent systemic therapies such as chemotherapy or immunotherapy. Patients should continue all regular medications and will need no additional medications because of the radiotherapy.

4.3.1 Analgesia dosing adjustments should not be made within the 1 week prior to initiation of radiotherapy.

4.4 Duration of Therapy

Treatment will last for 2 consecutive business days.

4.5 Removal of Patients from Protocol Therapy

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation of treatment will be documented and may include:

- Patient withdraws consent (follow-up);
- Patient is unable to comply with protocol requirements;
- Treating physician determines continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- The patient cannot be located and follow-up questionnaires cannot be obtained despite multiple attempts (which will be documented) after 12 months.

4.6 Duration of Follow Up

Patients will be followed for 6 months from the completion of RT to complete pain and QOL questionnaires. Patients can complete questionnaires in the clinic or over the phone.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Medical history*

Complete medical and surgical history, history of prior radiotherapy

5.1.2 *Demographics*

Age, gender, race, ethnicity

5.1.3 *Review subject eligibility criteria*

Review previous and concomitant medications

5.1.4 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.5 *Performance status*

Performance status evaluated prior to study entry.

5.1.6 *Pain and QOL assessment*

Baseline pain will be assessed using the BPI, EORTC QLQ-BM22 and EORTC QLQ-C30.

5.1.7 *Blood draw*

No blood draws are required for this protocol. Lab work will be recorded, if performed during the trial period. Lab work to be recorded includes cytogenetics (t(4;14), t(14;16), 17p13, 1q21 gain, monosomy/deletion chromosome 13) from diagnosis as well as IMWG response criteria labs (FLC levels, Serum and urine M-component, Bone marrow plasma cell percentage, Serum calcium, Serum B2M), and Plasma cell labeling index.

5.1.8 *Pregnancy test (for females of child bearing potential)*

Females of child bearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirement apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women of ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses> 1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

5.1.9 *Bone survey, CT, MRI or PET scan*

To be performed within 60 days of trial entry

5.1.10 Baseline AE Assessment-

5.2 Procedures During Treatment

5.2.1 On Treatment Visit at the end of therapy (day 2)

- Physical exam
- Vital signs
- Performance Status
- Record systemic therapy dosage and changes within 4 weeks
- BPI, EORTC QLQ-C30, EORTC QLQ-BM22

- Adverse event evaluation
  This dose of radiation should not produce any toxicities as radiotherapy side effects are related to dose. However, the treating physician should record toxicity, if seen, based on the location of treatment based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0) at the end of treatment and at all follow-up visits.

5.2.2 2 weeks, 4 weeks, 8 weeks and 6 months after treatment

- Performance Status
- Adverse event evaluation
- Record IMWG labs/response criteria, if available
- Record systemic therapy dosage and changes within 4 weeks
- BPI, EORTC QLQ-C30, EORTC QLQ-BM22

5.3 Follow-up Procedures

Patients will be followed at 2 weeks (+/- 1 week), 4 weeks (+/- 1 week), 8 weeks (+/- 1 week) and 6 months (+/- 2 weeks) after treatment. The patient should follow-up with hematology on their regular schedule. Patient can initiate additional follow-ups as needed. All follow-ups including D2-RT Questionnaires can be done over the telephone.

5.4 Study Calendar

	Within 30 days prior to the start of treatment	Within 3 days **prior to the start of RT**	Day 2of RT	2 weeks (+/- 1 week) after RT	4 weeks (+/- 1 week) after RT	8 weeks (+/- 1 week) after RT	6 months (+/- 2 weeks) after RT
Assessment	X						
Informed Consent	X						
Medical History	X						
Physical Exam	X		X				
Bone survey, CT, MRI or PET scan	X*						
Record cytogenetics, if available	X						
Record IMWG labs/response criteria, if available	X			X	X	X	X
Concomitant Treatments: Record systemic therapy dosage and changes within 4 weeks	X		X	X	X	X	X
Vital signs, (temperature, pulse, respiration, blood pressure) Height and Weight	X		X				
Performance Status	X		X	X#	X#	X#	X#
Pregnancy Test, if applicable**- urine or serum- per institutional policy	X						
Toxicity assessment		X	X	X	X	X	X
BPI^	X		X^^	X	X	X	X
Record Analgesic usage and dosage		X		X	X	X	X
EORTC QLQ-BM22^ and EORTC QLQ-C30		X	X^^	X	X	X	X

*** within 60 days of trial entry**

**** females of child bearing potential- see section 5.19**

^ Answers to the questionnaires should be regarding the INDEX lesion. Please complete one BPI and EORTC QLQ-BM22 per index lesion receiving treatment.

^^ Post RT-D2 questionnaires can be completed by telephone D2 treatment date + 1 day
 # Optional

Note:

If the patient requires second course of RT to the same index lesion(s) at standard dosing because of PP or IR after the 4-week mark, the patient will restart the follow up period: at 2 weeks, 4 weeks, 8 weeks and 6 months from the end of the second course of RT (including all questionnaires and assessments).

6.0 Measurement of Effect

6.1 Pain response

Term	Definition
Complete response (CR)	A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalent (OMED))
Partial response (PR)	Pain reduction in 2 or more at the treated site on a scale of 0-10 without analgesic increase, or analgesic reduction of 25% of more from baseline without an increase in pain
Pain progression (PP)	Increase in pain score of 2 or more above baseline at the treated site with stable OMED or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline
Indeterminate response (IR)	Any response that is not captured by the CR, PR or PP definitions[28]

Pain scores used to assess treatment response will be the average pain score (average of questions 3 through 6 on the BPI)). This will be assessed per index lesion identified at study entry.

Please see study calendar (5.4) for time points that BPI, EORTC QLQ-BM22 and EORTC QLQ-C30 and analgesic usage/dosage will be captured.

Time to pain response and duration of response will be assessed by regularly scheduled questionnaires (baseline, 2, 4, 8 weeks and 6 months after completion of RT).

Patients will be required to complete the questionnaire, either in the clinic, or over the telephone.

The **duration of pain response** is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive pain is objectively documented.

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event related to study treatment, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- there is a satisfactory explanation other than the study treatment for the changes observed; or
- death.

7.2 Definitions

7.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 Severity of Adverse Events

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.3.3.1 Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself. Death within 30 days of last treatment date should be reported as an event. Death beyond that point does not require reporting.

7.3.3.2 Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.3.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.3.3.4 Results in persistent or significant disability or incapacity.

7.3.3.5 Is a congenital anomaly/birth defect

7.3.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- 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 *unlikely related* to the study treatment.
- Unrelated – The AE is *clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the treatment.

7.4 Reporting Requirements for Adverse Events

7.4.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study treatment.
- An SAE occurring after consent but before first dose will not require expedited reporting

- The Institutional IRB must be notified of "any unanticipated problems involving risk to subjects or others" in accordance with the Institutional policy. Such policies will be provided to the CISO QA prior to enrolling 1st patient. (for USC refer to HSPP Policies and Procedures chapter 14 available at http://www.usc.edu/admin/oprs/policies/hspp.html UPR/UPIRSO).
- The USC NCCC Data and Safety Monitoring Committee (DSMC) must be notified within 24 hours of submission of such reportable event to the IRB. The patient ID and the study number as well as identifier of the SAE report should be submitted to the DSMC Coordinator via email or Fax to the attention of the DSMC Coordinator at 323-865-0089.

o All participating sites are required to complete the MedWatch 3500A for reporting. For all external sites please be sure to notify the study chair and CISO Multisite Coordinating Center.

7.4.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission. For studies requiring USC DSMC review, this report should also be forwarded to the DSMC Coordinator. If USC holds the IND, a list of all toxicities will be included in the IND annual report.

8.0 STATISTICAL CONSIDERATIONS

This is a single arm Phase II study to assess the efficacy of 2Gy x 2 radiation treatment to painful bone lesions in patients with multiple myeloma with the primary aim of determining whether this regimen achieves adequate pain control.

8.1 Study Endpoints

The primary analytic endpoint is pain response (section 6.1) of CR or PR at 4 weeks from treatment in the reference lesion. Patients who withdraw consent or are lost to follow-up prior to the 4-week evaluation for reasons not unequivocally unrelated to inadequate pain control will be considered pain control failures (i.e. pain progression). Patients who receive less than the 2Gy x 2 radiation treatment for reasons unequivocally unrelated to inadequate pain control will not be evaluable and will be replaced.

Secondary endpoints include pain response at 2 weeks, 8 weeks, and 6 months, analgesic use, EORTC QLQ-BM22 and EORTC QLQ-C30 QOL score, and time to pain response and duration of response.

8.2 Sample Size and Accrual

A total of 100 evaluable patients will be enrolled.

8.3 Study design and analytic plan

8.3.1 Analytic plan for primary objective

This study will be a two-stage Phase II design. Current standard of care treatment results in pain response at 4 weeks in approximately 80-85% of patients. In the context of the 2Gy x 2 reduced dose treatment regimen, achieving pain response in at least 70% of patients will be sufficient to consider this a viable treatment approach. A pain response rate of 55% or less will be considered inadequate.

A total of 100 patients will be enrolled in two stages. In the initial stage, after the 40th patient has been enrollment, study enrollment will be suspended pending assessment of pain response in all patients for futility analysis

- A minimum of 22 of 40 patients achieving pain response of CR or PR at 4 weeks will be required to continue enrollment to 100 patients.
- A minimum of 64 of 100 patients achieving pain response of CR or PR at 4 weeks will be required to conclude that 2Gy x 2 treatment is effective in a sufficient proportion of patients treated.

With a null hypothesis pain response rate of 55%, this design has Type I error of 0.042, and power of at least 0.91 for a pain response rate of 70%. If the true pain response rate is 55% there is a probability of 0.43 that the first stage criterion for continue will not be satisfied.

If the study continues to completion, the pain response rate will be estimated with a standard error no greater than ± 0.05.

8.3.2 Analytic plan for secondary objectives

8.3.2.1 **Assess Quality of life**

The average EORTC QLQ-BM22 and QLQ-30 score will be assessed at baseline, and at day 2 and 2, 4, 8, and 24 weeks from treatment. Average QOL score at each time point will be computed, appropriately accounting for patients who will have been re-treated for pain symptoms in the intervening period. Analysis of variance or linear regression analysis will be used to determine whether any factors, such as sex, age, or disease stage, are associated with this QOL measure.

8.3.2.2 **Assess analgesic use/reduction**

The average morphine equivalent dose of analgesic used will be assessed at baseline, and at day 2 and 2, 4, 8, and 24 weeks from treatment. Average dose at each time point will be computed, appropriately accounting for patients who will have been re-treated for pain symptoms. Analysis of variance or linear regression analysis will be used to determine whether any factors, such as sex, age, or disease stage, are associated with this analgesic dose.

8.3.2.3 **Measure time to pain relief and duration of pain relief**

Time to and duration of pain relief will be assessed, and will be analyzed using survival analysis methods. The analysis will assess whether any factors, such as sex, age, or disease stage, affect these measures. Additional treatment for pain prior to any pain progression will be considered a time-dependent covariate in these analyses, while additional treatment in response to any pain progression will be considered pain control failures in these analyses.

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

All investigators will follow the University conflict of interest policy. Any USC investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must complete a “Statement of Outside Interests Related to Research” Form. The application is reviewed and approved by the Conflict of Interest Review Committee (CIRC) USC conflict of interest policy is available at http://ooc.usc.edu/conflict-interest-research

9.2 Institutional Review Board (IRB) Approval and Consent Process

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol and all study related documents used in the study (e.g. QOL questionnaire, pill diary, brochure, advertisement etc).

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing a dated IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person authorized to obtain the informed consent

9.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Investigation Support Office (CISO)

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Protocol signature page with Investigator signature
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND.
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.4 Registration Procedures

Multi-Site Registration:

All participants in the multi-site trial are subject to central registration, which is used for tracking study accrual, checking eligibility, and monitoring adequate participation of women and minorities. Subject registration will be conducted through the coordinating center at the NCCC-CISO. External sites will identify eligible subjects and verify enrollment availability with the MCC prior to consenting patients. The external site is required to notify the MCC of a new signed informed consent within 48 business hours and note the basic consent information on the screening log. A copy of the consent will accompany the complete eligibility packet for verification. The MCC will enter the patient, demographic, and consent information in the applicable USC database. The MCC will assign a study patient sequence ID and communicate this to the external site.

The Coordinating Center Program Hours are 8 am to 4 pm, Monday through Friday, based on the PST zone. The MCC will be closed on official government holidays unless otherwise indicated. The contact number for the MCC is 323-865-3122. A copy of the registration sheet is located in the Appendix.

External sites will verify eligibility prior to submitting documents to the MCC for central registration. External sites must submit registration requests to the MCC at least one full business day prior to the planned treatment start date. Registration will require the external site to submit to the MCC all of the following:

- A completed registration form with patient demographics:
- Zip code
- Age
- Sex
- Race
- Ethnicity
- Initials
- Date of Birth (DOB)
- A completed Eligibility Checklist signed by the investigator
- A copy of the most recently IRB-approved, patient signed informed consent form
- All required screening tests, within the time parameters specified by the protocol study calendar
- All other de-identified source documents needed to verify all points of eligibility
- Any On-Study forms for registration specified by protocol

These documents must be securely emailed to the MCC staff. With advance notice documents will also be accepted faxed to 323-865-0457. The MCC will verify completeness of documents and confirm eligibility. The MCC will enter the registration information in the USC OnCore® database. The MCC will then fax or securely email the completed Registration Form with the assigned study sequence ID to the external site as confirmation of patient registration.
An external site must maintain a log of all subjects who sign informed consents. The log must also document an explanation for exclusion due to screen failure. The MCC will provide sites with a Patient Tracking Log at the time of site activation. In the event of screen failure, external sites must submit the Screen Failure form to the MCC within one business day of determining screen failure.

Participating sites are required to retain, in a confidential manner, sufficient information on each subject so that the subject may be contacted should the need arise.

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology reports, MRI reports, Operative reports, etc.) submitted to the CISO-MCC must have the patient's full name and social security number redacted (blacked out) and the assigned CISO-MCC patient ID number, protocol number, and site number written in. Patient initials only may be included or retained for cross verification of identification.

A registration verification letter will be emailed (preferred) or faxed to the registering site within one working day for patients registered to CISO-MCC multi-site trials. Treatment may not be initiated until the site receives this faxed or emailed verification.**USC Registration:**
For patients enrolled at USC, the Research Coordinator must complete the protocol eligibility form to ensure that the patient is eligible. The PI will review the patient eligibility (with assistance from the Research Coordinator- who will assemble the required source documents, and do an initial review) prior to registering the patient on study.

The Research Coordinator or data manager will then register the patient into the Cancer Center database, Café, by accessing the Registration forms. Likewise, after the patient has completed the study, the Off Study forms in cafe will need to be completed, for Off Treatment and Off Study.

9.5 RECORDS AND DATA SUBMISSION

A. Confidentiality of Records

The original data collection forms will be kept in secure file cabinets, for USC patients forms will be kept in the Clinical Investigations Support Office (CISO).

B. Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent with the Human Rights and the HIPAA authorization must be given to the patient. Institutional policy regarding distribution and location of original consent documents should be followed. When a study is opened at two or more institutions, a copy of the signed consent and HIPAA should be sent to USC CISO QA team as soon as possible, and not later than within 5 business days of obtaining consent. For patients consented at USC/LAC, institutional policy should be followed: a copy of ICF and HIPAA should be uploaded through True to USC CRO and to CISO QA Team. The original will be kept in the patient research chart maintained by the study assigned Data Manager.

C. Registration Eligibility Worksheet

At the time of registration, the completed Eligibility Worksheet will be submitted to the QA Monitor at CISO for review of eligibility compliance.

D. Data Collection Forms and Submission Schedule

If a treatment trial, protocol data will be entered into eCRFs in MEDIDATA.
Within two weeks of registration, the data manager will complete the initial set of On Study forms and baseline Toxicities
Within two weeks of completion of each course of treatment, the data manager must complete the Course Assessment, Toxicities, and if appropriate Response data.

- After Off Treatment, within two weeks of each follow up, complete the Follow Up forms.

9.6 Data Management and Monitoring/Auditing

9.6.1 Active Monitoring Program Details

a. **Adherence to Protocol/Per Patient**: It is the responsibility of the USC Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at USC are all performed as specified in the protocol. When a study is opened at two or more institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

b. **Day-to-Day Monitoring – Eligibility:** At USC, the Study Coordinator will assist the Investigator in reviewing eligibility and will assemble the required source documents, and do a final review by completing an Eligibility Registration Worksheet. When a study is opened at two or more institutions, the PI at each institution will review the patient eligibility in accordance with that institution's policy. For all institutions, the Eligibility Registration Worksheet with a copy of Informed Consent and supporting source documents will be submitted to CISO QA via email or Fax for verification prior to registering the patient on study.

c. **Day-to-Day Monitoring – Informed Consent:** Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. A copy of the ICF will also be provided to CISO QA for review. CISO SOP 3.3 will be followed.

d. **Day-to-Day Monitoring – Treatment:** The PI and co-investigators are responsible for ensuring that treatment is given per protocol. The Study

Coordinator will review the treatment orders with the treating investigator. Regardless of who the treating physician is, there will be only one responsible Study Coordinator for each study at each of the hospitals affiliated with the USC Norris Cancer Center. The treating investigator will review the status of each patient on-study, with the Study Coordinator and treating physicians, on an on-going basis. When a study is opened at two or more institutions, CISO QA will periodically audit medical records for the subjects on study at other institutions to ensure compliance and adherence to the protocol.

e. **Data Management – Patient Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, All written source documents not associated with the study research are maintained in the patient chart, which is stored in the Department of Medical Records at the appropriate hospital. At the Norris Hospital, the official medical record is the Electronic Patient File (EPF). Radiographical images are stored in the Department of Radiology and in an electronic system called Synapse. At Los Angeles County General Hospital the official medical record is called Affinity. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patients' hospital charts. It is the responsibility of the research staff to ensure that the patient chart contains the required documents and work closely with treating investigators to ensure all protocol-related assessments are carefully documented.

f. **Data Management – Research Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, to facilitate adherence to the protocol schedule and data management, research charts are created to collect copies of the relevant notes, orders and results, that are in the Patient Chart. In Addition, all source documents related to the research, such as original informed consent forms, HIPAA Forms, AE assessment worksheets, disease response worksheets and NTFs are maintained in the Research Charts. Protocol calendars, worksheets, and checklists, are also kept in the research chart. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site. It is the responsibility of the Data Manager to ensure that the research chart contains all the required documents.

g. **Data Management – Case Report Forms:** It is the responsibility of the Data Manager to complete the required case report forms. For in-house trials, case report forms are developed for each trial; these are used to finalize the data entry screens in the Cancer Center clinical trials database. It is the responsibility of the PI to review the Off-Study Summary form which summarizes pertinent toxicity, response and adherence information, once the patient has completed treatment.

9.6.2 Quality Assurance Monitoring Committee (QAMC) Oversight

The Quality Assurance and Monitoring Committee (QAMC) of the NCCC has the responsibility for study auditing and monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual. QAMC procedures are detailed in the NCCC Data Safety and Monitoring Plan available on CISO Website.

9.6.2.1 QAMC Annual Patient Audits

The QAMC is responsible for conducting audits and providing the initial review of the audits, for all open institutional (i.e. USC

initiated), CCCP-sponsored trials, and any trials identified by the CIC. These trials are audited by the QAMC once a year. Faculty and staff at the Cancer Center involved in clinical research – but not directly involved in the research under evaluation – are asked to serve as auditors. Twenty percent of patients accrued during the past 12 months – and a minimum of 2 patients – are selected at random; however, additional patients may be selected for audit if there is some indication that there might have been a problem or unusual circumstance (possibly related to compliance, toxicity, response or some indication of an irregularity). The audit involves a review of the research chart, hospital medical record (i.e., source documentation) and evaluates the following: documentation of eligibility (including failure to obtain appropriate informed consent) and baseline status of the patient; documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome. In addition, for investigative agents, a drug audit is also performed for these patients by the Research Pharmacist. In addition, for Institutional, Investigator Initiated Trials, Data in the CAFÉ database are compared to the information in the medical record.

9.6.2.2 QAMC Annual Protocol Review

All open trials are reviewed at least once a year by the QAMC (or more often if stipulated by the CIC). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual; examination of gender and minority accrual; examination of all reported violations; review of past audits and correspondence with the PI; review of results of current audit (by an outside agency or by the NCCC QAMC); review of previous correspondence between the PI and the QAMC/DSMC. The QAMC review process is detailed in USC NCCC DSM Plan available on the CISO website.

9.6.3 Data and Safety Monitoring Committee (DSMC) Oversight

The Data and Safety Monitoring Committee (DSMC) is an independent body responsible for the safety of study subjects through the review of new protocols to ensure an adequate adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials. DSMC procedures are detailed in USC NCCC DSM Plan available on the CISO website.

9.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

9.7.2 Non-Emergency departures from protocol

A protocol deviation is any variance from an IRB approved protocol.
If the deviation meets all of the following criteria, it is considered a minor protocol deviation that:

- Is generally noted or recognized only after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

If the deviation meets any of the following criteria, it is considered a protocol violation:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: All protocol violations will be entered in the clinical trial database by the Research Coordinator. In addition, Research Coordinator and Investigator should report all protocol violations within one (1) week of the knowledge of the event using iStar.

9.7.3 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB as well as to all the sponsoring agencies (FDA, NCI, etc.) for review and for approval prior to implementation. It is the responsibility of the study PI to ensure that the appropriate agencies have been informed of the proposed amendments and that these have been reviewed and approved.

9.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other

cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

1. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol.* 2013;31(18):2347-2357.
2. Shin SM, Chouake RJ, Sanfilippo NJ, et al. Feasibility and efficacy of local radiotherapy with concurrent novel agents in patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2014;14(6):480-484.
3. Balducci M, Chiesa S, Manfrida S, et al. Impact of radiotherapy on pain relief and recalcification in plasma cell neoplasms: long-term experience. *Strahlenther Onkol.* 2011;187(2):114-119.
4. Matuschek C, Ochtrop TA, Bölke E, et al. Effects of Radiotherapy in the treatment of multiple myeloma: a retrospective analysis of a Single Institution. *Radiat Oncol.* 2015;10:71.
5. Lee JW, Lee JE. Local radiotherapy for palliation in multiple myeloma patients with symptomatic bone lesions. *Radiat Oncol J.* 2016;34(1):59-63.
6. Rudzianskiene M, Inciura A, Gerbutavicius R, et al. Single vs. multiple fraction regimens for palliative radiotherapy treatment of multiple myeloma : A prospective randomised study. *Strahlenther Onkol.* 2017;193(9):742-749.
7. Mill WB, Griffith R. The role of radiation therapy in the management of plasma cell tumors. *Cancer.* 1980;45(4):647-652.
8. Glück S, Van Dyk J, Messner HA. Radiosensitivity of human clonogenic myeloma cells and normal bone marrow precursors: effect of different dose rates and fractionation. *Int J Radiat Oncol Biol Phys.* 1994;28(4):877-882.
9. Deacon J, Peckham MJ, Steel GG. The radioresponsiveness of human tumours and the initial slope of the cell survival curve. *Radiother Oncol.* 1984;2(4):317-323.
10. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood.* 2016;127(24):2955-2962.
11. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. *Cancer.* 1982;50(5):893-899.
12. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. *Cancer.* 1985;55(7):1468-1472.
13. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst.* 2005;97(11):798-804.
14. Howell DD, James JL, Hartsell WF, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. *Cancer.* 2013;119(4):888-896.
15. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol.* 2007;25(11):1423-1436.
16. Tsang R, Campbell B, Goda J, et al. Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines from the International Lymphoma Radiation Oncology Group. In. Vol 101: International Journal of Radiation Oncology Biology and Physics; 2018:794-808.
17. Society AC. Rates by Stage for Multiple Myeloma. https://www.cancer.org/cancer/multiple-myeloma/detection-diagnosis-staging/survival-rates.html. Published 2018. Accessed June 25, 2018, 2018.
18. Shimizu T, Motoji T, Oshimi K, Mizoguchi H. Proliferative state and radiosensitivity of human myeloma stem cells. *Br J Cancer.* 1982;45(5):679-683.
19. Bosch A, Frias Z. Radiotherapy in the treatment of multiple myeloma. *Int J Radiat Oncol Biol Phys.* 1988;15(6):1363-1369.
20. Leigh BR, Kurtts TA, Mack CF, Matzner MB, Shimm DS. Radiation therapy for the palliation of multiple myeloma. *Int J Radiat Oncol Biol Phys.* 1993;25(5):801-804.
21. Girinsky T, Guillot-Vals D, Koscielny S, et al. A high and sustained response rate in refractory or relapsing low-grade lymphoma masses after low-dose radiation: analysis of predictive parameters of response to treatment. *Int J Radiat Oncol Biol Phys.* 2001;51(1):148-155.
22. Ganem G, Lambin P, Socié G, et al. Potential role for low dose limited-field radiation therapy (2 x 2 grays) in advanced low-grade non-Hodgkin's lymphomas. *Hematol Oncol.* 1994;12(1):1-8.

23. Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. *J Clin Oncol.* 2003;21(13):2474-2480.
24. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain.* 1983;17(2):197-210.
25. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain.* 1995;61(2):277-284.
26. McDonald R, Ding K, Brundage M, et al. Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. *JAMA Oncol.* 2017;3(7):953-959.
27. Chow E, Nguyen J, Zhang L, et al. International field testing of the reliability and validity of the EORTC QLQ-BM22 module to assess health-related quality of life in patients with bone metastases. *Cancer.* 2012;118(5):1457-1465.
28. Chow E, Hoskin P, Mitera G, et al. Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Int J Radiat Oncol Biol Phys.* 2012;82(5):1730-1737.
29. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia.* 2009;23(1):3-9.
30. Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia.* 2014;28(2):269-277.