

**A pilot study of combined decompressive spine radiosurgery and pembrolizumab
in patients with high-grade epidural disease**

Wake Forest Baptist Comprehensive Cancer Center
WFBCCC #03321

Principal Investigator: *Christina K. Cramer, MD*
Department of Radiation Oncology

Co-Investigator(s): *Michael Farris, MD*
Department of Radiation Oncology

James D. Ververs, Ph.D.
Department of Radiation Oncology

Wesley Hsu, MD
Department of Neurosurgery

Stacey Quintero Wolfe, MD
Department of Neurological Surgery

Thomas G. West, MD
Department of Radiology

Yusuke Shiozawa, MD, PhD
Department of Cancer Biology

Biostatistician *Fang-Chi Hsu, PhD*
Department of Biostatistics and Data Science

Study Coordinator: *Ashley Fansler*

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Regulatory Contact:

Emily Teal
[REDACTED]

Protocol Editor:

Mac Robinson
[REDACTED]

Participating Institution(s):

Comprehensive Cancer Center
Wake Forest University
Department of Radiation Oncology
Medical Center Blvd.
Winston-Salem, NC 27157

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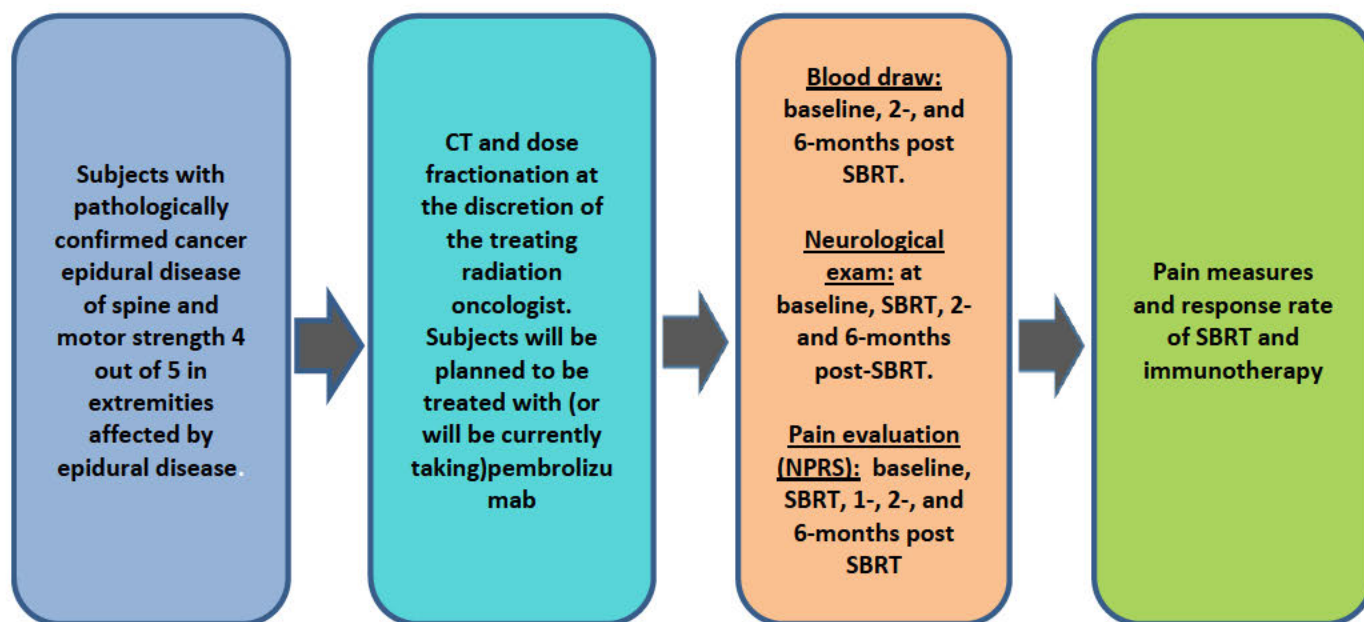
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SCHEMA



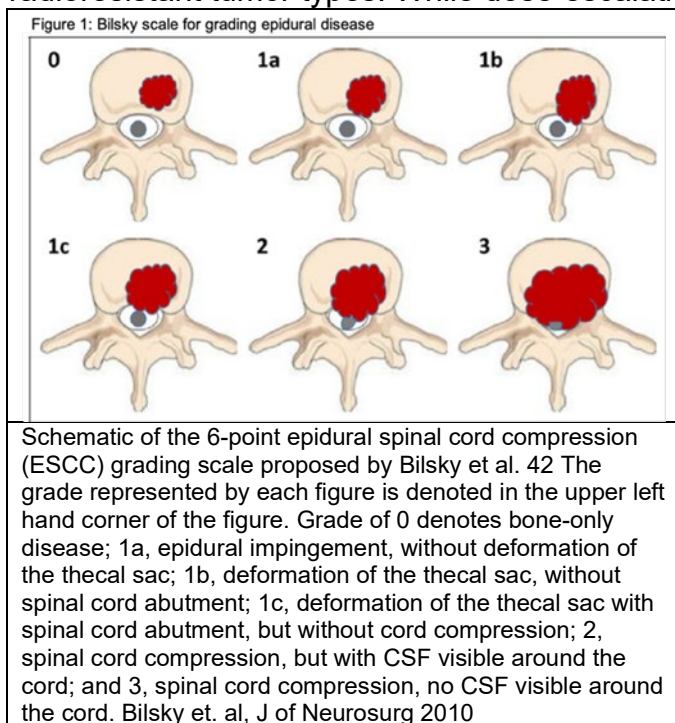
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1.0 Introduction and Background

An estimated 300,000 adult patients in the United States have osseous metastases and 60% of these are estimated to be spinal metastases¹. Some of these metastases are confined to the bone but approximately 20% develop malignant epidural spinal cord compression (MESCC)² where the disease enters the spinal canal. In addition to causing pain, this places patients at risk for neurologic compromise. In mild cases, epidural disease may be visible but not causing any symptoms. In severe cases, epidural disease can compress the spinal cord and cause numbness, paralysis (paraplegia or quadriplegia depending on the level effected), and loss of control of bladder and bowel functions.

Historically, MESCC has been managed with either surgery followed by 10 treatments of radiation (conventionally-fractionated external beam radiotherapy (EBRT)) or radiation alone for patients who are non-operative candidates, however the advent of Stereotactic Body Radiotherapy (SBRT) over the past two decades, has challenged this paradigm. SBRT implies delivering RT in 5 or fewer fractions with more precise treatment techniques. Higher doses per treatment kill a larger proportion of tumor cells. For spinal metastases, SBRT improves local control and the rate of pain relief. Notably, treatment appears to be more durable compared to conventionally-fractionated EBRT for patients with more radioresistant tumor types. While dose-escalation has advantages in terms of tumor



control, there is also a higher risk of inducing radiation myelitis with SBRT than with standard EBRT. Radiation myelitis is damage to the spinal cord from RT causing neurologic compromise and can only be diagnosed once progressive tumor has been ruled out. It is a rare but devastating complication of treatment. Consequently, spine SBRT is considered a “high risk and high reward” treatment strategy that is undertaken in highly selected patients.

Generally, epidural disease closer than 2 to 3mm from the spinal cord is regarded as a contraindication to spine SBRT in order to minimize the risk of radiation myelitis. The extent of epidural disease is often graded using the Bilsky Scale (see figure 1). For high-grade epidural disease

(i.e. Bilsky grade 1c, 2 and 3) current consensus guidelines recommend surgical decompression followed by either conventionally fractionated EBRT for radiosensitive histologies or post-operative SBRT for radioresistant histologies^{2,3}. However, many patients (who by these guidelines would be recommended to have surgery followed by post-operative SBRT) are poor surgical candidates due to medical co-morbidities or widespread disease. Patients whose disease is closer than 2mm to the spinal cord often receive EBRT rather than SBRT, missing out on the potential for the increased accuracy and efficacy

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shown by SBRT. A few expert centers use decompressive SBRT in a single fraction for high-grade epidural disease^{4,5} but this technique has not been incorporated into treatment algorithms or guidelines^{2,3}. Decompressive SBRT essentially amounts to delivering SBRT in patients where the epidural disease is closer than 2mm to the spinal cord in an attempt to reduce compression of the spinal cord and increase the patency of the thecal sac.

Figure 2: patient treated with decompressive SBRT and immunotherapy

In 2010 Ryu et al. published a prospective, phase II trial of 62 patients treated with single-session decompressive radiosurgery⁴. In the patients with available pre and post-treatment MRI imaging, the percentage of thecal sac patency was calculated as the ratio of the thecal sac area at the level of greatest epidural disease to the estimated pre-compression thecal sac area. The estimated pre-compression thecal sac area was calculated by averaging the area of the thecal sac at one spinal level above and one spinal level below the level of the compression. Thecal sac patency was increased from 55% to 76% at 2 months after radiosurgery. Treatment was well-tolerated with no cases of radiation myelitis.

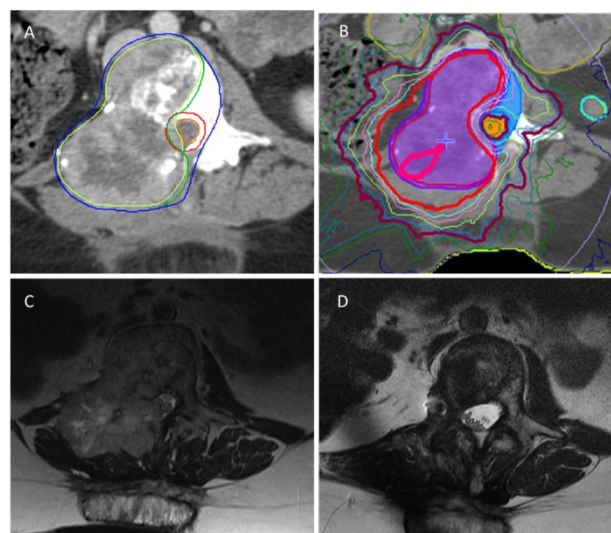


Figure 2: a) The blue line is the PTV19. Light green is GTV and dark green is the PTV30 which is shaved 3 mm away from the thecal sac/cauda (orange). b) Single-arc VMAT plan. 30 Gy isodose line in red and 19 Gy isodose line in deep purple. c) T2-weighted MRI before treatment. d) T2-weighted MRI 18 months after treatment.

We recently published a case report of a patient who received five-fraction decompressive SBRT followed by immunotherapy treatment.⁶ Using this same quantification strategy as Ryu et al., our patient had an improvement in thecal sac patency from 47% to 99%. Since the magnitude of her response was greater than that reported with either radiosurgery or immunotherapy alone, we hypothesized that radiosurgery and immunotherapy acted synergistically to yield a response better than would be expected with either modality alone. In our recent publication, we suggest that studies need to be undertaken to evaluate whether decompressive SBRT is more effective in patients receiving immunotherapy.

The potential benefits of combined immunotherapy and SBRT is arguably one of the most exciting topics in oncology. Radiation helps activate the immune system by increasing antigen expression, upregulating immunogenic cell surface markers, increasing secretion of cytokines, inducing immunogenic cell death, improving antigen presentation, increasing expression of PD-L1, and depleting immunosuppressive cells.⁷ Yet there has been minimal discussion of immunotherapy and SBRT in the context of high-grade epidural disease. If combined modality treatment makes decompressive SBRT more effective, then treatment algorithms need to be updated to encourage the utilization of decompressive SBRT in patients who are slated to receive subsequent immunotherapy. Combining immunotherapy and RT has been done safely in multiple settings but the most relevant data in this setting is a recent phase II trial (the PEMBRO-RT trial) that included patients with metastatic

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lesions in multiple sites including the spine. In this 92-patient study, pembrolizumab following SBRT was well-tolerated and there were no cases of myelitis reported.⁸

2.0 Objectives

The primary aim of this pilot trial is to determine the feasibility of delivering spine SBRT and at least one cycles of pembrolizumab for spinal metastases associated with high-grade epidural disease. The secondary objective is to determine if decompressive SBRT with pembrolizumab leads to a higher radiographic response rate (i.e., improvement in thecal sac patency) than decompressive SBRT alone. Additional exploratory aims will be to evaluate accrual rate, pain relief rate, toxicity, and potential correlative blood biomarkers.

2.1 Primary Objective

2.1.1 To determine the feasibility of patients completing SBRT and at least 1 cycle of pembrolizumab.

2.2 Secondary Objectives

2.2.1 Evaluate the radiographic response after decompressive SBRT and pembrolizumab by calculating the improvement in thecal sac patency (see 5.2.1).

2.2.2 Evaluate accrual rate,

2.2.3 Evaluate pain relief.

2.2.4 Evaluate quality of life.

2.2.5 Evaluate cumulative incidence of adverse events.

2.2.6 Evaluate potential correlative blood biomarkers.

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3.0 Patient Selection

In the previously discussed phase II study by Ryu et al., patients were eligible if they had a pathologically-confirmed diagnosis of cancer, epidural disease of the spine seen on MRI or CT (restricted to 1 or 2 contiguous spinal cord levels), and motor strength of 4 out of 5 on physical exam in the extremities affected by the epidural disease. No restriction was placed on patient performance status. For this study, we will match this population as closely as possible but with the additional stipulation that the patient must be receiving or anticipated to receive at least one dose of pembrolizumab within 6 weeks after finishing SBRT. A summary of inclusion and exclusion criteria are below. All are identical to the historical cohort provided by Ryu et al. with the exception that our cohort will receive pembrolizumab. All enrolled patients will be reviewed by both a radiation oncologist and neurosurgeon to ensure that the patient is eligible.

3.1 Inclusion Criteria

- 3.1.1 Pathologic diagnosis of cancer, confirmed by review of pathology report.
- 3.1.2 Epidural disease seen on MRI at 1 vertebral level or 2 contiguous vertebral level.
- 3.1.3 Synchronous and metachronous sites of disease allowed.
- 3.1.4 Patient with expected life span of ≥ 3 months.
- 3.1.5 Deemed eligible for SBRT and pembrolizumab after multi-disciplinary review. The multi-disciplinary review will be conducted virtually via our SPinal Oncology Group (SPOG) Wake Forest e-mail listserv. Members of the distribution list include neurosurgeons, orthopedic surgeons, interventional radiologists, radiologists, and radiation oncologists. This group meets monthly via webex and in the interim, cases are routinely reviewed using encrypted emails via the listserv. Because we will not be able to wait for a month meeting to enroll patients on study, we anticipate needing to review these patients via the listserv. The electronic review will serve as documentation of multi-disciplinary review.
- 3.1.6 Patients currently being treated with pembrolizumab or anticipated to receive at least one dose of pembrolizumab within six weeks after finishing SBRT.
- 3.1.7 Patients who have received prior immunotherapy are allowed.
- 3.1.8 Age equal or greater than 18.
- 3.1.9 Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative).

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3.2 Exclusion Criteria

- 3.2.1 Prior RT or surgery to index lesion.
- 3.2.2 Patients with lymphoma, multiple myeloma, germinomas, seminomas, Wilm's tumors, and Ewing's sarcomas will be excluded.
- 3.2.3 Muscle strength of ≤ 3 out of 5 on neurologic exam that correlates with level of the involved spinal cord.
- 3.2.4 Retropulsed compression fracture.
- 3.2.5 Patients with a contraindication to pembrolizumab.
- 3.2.6 Patients may not be receiving any other investigational agents.
- 3.2.7 Patients with symptomatic, brain metastases, as determined by the study PI, that could confound the neurologic exam, should be excluded.
- 3.2.8 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.9 Pregnant women are excluded from this study because both radiation and pembrolizumab can be harmful to the developing fetus. Because there is an unknown but potential risk for adverse events, pregnant women are not allowed to participate in this study, in nursing infants secondary to treatment of the mother with pembrolizumab, breastfeeding should be discontinued.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

The study consent form will also be provided in Spanish for Spanish-speaking participants. Based on WFBCCC population estimates, we expect approximately 45% of participants to be women. Translating this to our sample size estimate of 10, we plan to enroll about at least 5 women. We plan to enroll at least 13% Black or African American (N=1). Due to the small sample size, we do not anticipate enrolling any one of Hispanic, American Indian/Alaska Native, or Asian background. However, all eligible subjects will be evaluated for inclusion. Should we not meet or exceed these estimates, the PI will engage the Office of Cancer Health Equity to discuss strategies to enhance recruitment in these target populations.

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4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist ([Appendix A](#))
2. Complete the Protocol Registration Form ([Appendix B](#))
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 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
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

- 5.1.1 The primary outcome is the proportion of feasibility which is defined as the proportion of patients completing both SBRT and at least one cycle of pembrolizumab.

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5.2 Secondary Outcomes

- 5.2.1 Thecal sac patency calculated as the area of the thecal sac mean improvement in thecal sac patency at 2 months and 6 months. The percentage of thecal sac patency, which will be calculated as the ratio of the thecal sac area at the level of greatest epidural disease to the estimated pre-compression thecal sac area. The estimated pre-compression thecal sac area will be calculated by averaging the area of the thecal sac at one spinal level above and one spinal level below the level of the compression. Thecal sac patency will be determined by a board-certified neuroradiologist who will be blinded to whether the MRI or myelogram image is pre- or post-treatment
- 5.2.2 Accrual rate will be calculated as the number of patients enrolled per month. We estimate one patient every 2 months.
- 5.2.3 Pain relief will be measured on the Numeric Pain Rating Scale (NPRS). The proportion of patients that experience the improvement in pain will be defined as below.¹

The proportion of patients that experience a clinically significant improvement in pain defined as either a 33% decrease in pain score or an absolute decrease from baseline of 2 points.⁹

- 5.2.4 Quality of life will be evaluated by EORTC QLQ-BM22. This is an internationally validated scale used to measure QOL in bone metastases patients. We selected changes of at least ten points from baseline to 2 months and baseline to 6 months represent a clinically meaningful change.¹⁰
- 5.2.5 Cumulative incidence of compression fracture (new or worsening after SBRT during the 6 month of study follow up), rate of pain flare by physician assessment during the first month after SBRT, cumulative incidence of radiation myelitis during the 6 month of follow up. Radiation myelitis will be defined by the study PI using clinical and radiographic techniques.
- 5.2.6 The baseline as well as 2- and 6-month post-SBRT plasma will be tested for histamine, Calcitonin gene-related peptide (CGRP), and substance P which will characterize bone turnover markers, specifically for N-terminal propeptide of type 1 procollagen (P1NP; bone formation) and C-terminal telopeptide of type 1 collagen (CTX; bone resorption).

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6.0 Intervention Plan

6.1 Study-Related Activities

	Pre-Study ^a	Baseline	SBRT	Pembrolizumab (Day 1 of each cycle)	1-month Post SBRT visit (phone or in office)	2-month Post SBRT follow up	6-month Post SBRT Follow-up
Informed consent	X						
Demographics	X						
Pre-toxicity	X						
Medical history	X						
Concurrent meds	X						
Neurologic Exam	X		X			X	X
Adverse Events			X	X	X	X	X
Vital signs	X	X		X		X	X
Height, Weight, M ²	X			X			
Performance Status	X					X	
CBC w/diff, platelets	X			X			X
Serum chemistry ^b	X			X			X
B-HCG ^c	X						
MRI/Thecal Sac Patency ^d		X				X	X
Pain Measurement Scale-(NPRS)		X	X ^g		X	X	X
Physician Assessment of Pain Flare ^f			X ^e		X	X	
Research blood draw		X				X	X
EORTC QLQ-BM22		X				X	X

a. Pre-study requirements listed in table must be completed **within** 10 days prior to registration.

b. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

c. Serum pregnancy test (women of childbearing potential).

d. ± 4 weeks

e. Can occur at any point during SBRT.

f. Physician determination. Any pain increases or exacerbation after treatment up to 2 months

g. Can be performed at any treatment visit during SBRT

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6.2 Intervention Administration

The intervention will be administered on an outpatient basis. Reported adverse events and potential risks related to the intervention are described in [Section 8.0](#).

6.3 Study Intervention and Treatment

6.3.1 SBRT

After enrollment, patients will undergo CT simulation and will be immobilized in either a BodyFix® or long thermoplastic mask depending on the location of the lesion. 1.25mm slices will be acquired (see study diagram below). For treatment planning, available diagnostic imaging will be fused with the planning CT scan. Patients must have either an MRI or CT myelogram or both for the purpose of treatment planning. Enrolling physicians can elect to do the myelogram on the day of the CT simulation and forego a diagnostic CT if patients will have their CT simulation within 3 hours of injection of intrathecal contrast. A gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) will be designed in accordance with published guidelines.^{11,12} The cord and/or thecal sac will be contoured on either the registered T2-weighted MRI or CT myelogram. Dose and fractionation will be at the discretion of the treating radiation oncologist (as will the constraint to the spinal cord). Treatment planning will be done in Elekta Monaco® and all plans will be reviewed by the study PI prior to treatment to ensure quality and will also be reviewed by the patient's neurosurgeon. Treatment will be delivered on an Elekta Axesse™ with cone beam CT (CBCT) prior to treatment delivery. Of note, all of this is considered routine and standard-of-care when undertaking spine SBRT.

6.3.2 Pembrolizumab Treatment

Pembrolizumab will be delivered at the discretion of the patient's medical oncologist within 6 weeks after finishing SBRT. If a patient is already receiving pembrolizumab at the time of enrollment, then SBRT should not start sooner than 5 days after the last pembrolizumab infusion.

6.3.3 Blood draws

Patients will have a blood draw at baseline and at 2-months post-SBRT, and 6 months post-SBRT.

Email notification will be sent to Sun Park [REDACTED], Kelly Contino [REDACTED], Macie Wilson [REDACTED], and Yusuke Shiozawa [REDACTED] the day before the blood collection.

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Blood will be collected in two green-top vacutainer tubes containing heparin (60 USP Units of Lithium Heparin/6ml tube), and immediately inverted 8-10 times to prevent coagulation. Attention: Protocol # and the Patient ID in addition to the other standard information should be on the tube.

Samples will then be transported from the Cancer Center to the Shiozawa lab [REDACTED].

6.3.4 Patient Reported Outcomes

Number Rating Pain Scale (NRPS) Pain Evaluation-The NRPS Pain Evaluation Scale is a validated instrument for obtaining patient-reported pain. Pain relief will be measured as in study outcomes section Secondary Outcomes 5.2.3. See attached forms.

QLQ-BM22-The EORTC QLQ-BM22 is a patient survey that evaluates quality of life for patients with bone metastases. This form has 22 questions. See attached forms.

6.3.5 Physician Rated Pain Flare

Physicians will use the Pain Flare form to evaluate patient pain at SBRT, 1 month, and 2 months after SBRT

6.4 General Concomitant Medication and Supportive Care Guidelines

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

6.5 Duration of the Intervention

In the absence of delays or modifications related to any concurrent treatment, or the intervention, the intervention will continue for six weeks after SBRT but may be discontinued for the following reasons:

- Disease progression that prevents continuation of SBRT and pembrolizumab
- Intercurrent illness or conditions that prevents further intervention,
- 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 intervention in the judgment of the investigator.

6.6 Duration of Follow Up

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Patients will be followed for six months after SBRT (see [table 6.1](#)).

6.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in [section 6.5](#) applies.

7.0 Dose Delays/Dose Modification Pembrolizumab

Dose delays and modifications in pembrolizumab will be made at the discretion of each patient's treating medical oncologist as per standard-of-care guidelines.

Toxicity grades are defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0

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8.0 Adverse Events List and Reporting Requirements

8.1 Adverse Event List for pembrolizumab

In general, immunotherapy has a risk (>10%) of developing autoimmune complication(s), such as inflammation of the thyroid (hypothyroidism or hyperthyroidism), colon (colitis), lungs (pneumonitis), liver (hepatitis), or pituitary gland (hypophysitis), which can lead to the symptoms noted below. Autoimmune complications can potentially be life-threatening or permanent. In some cases they may be reversible with urgent administration of steroids and/or other immunosuppressant(s).	
More common (>10% of patients): • constipation • depressed mood • diarrhea • dry skin and hair • feeling cold • flushing • hair loss • hoarseness or husky voice • joint or muscle pain • muscle cramps or stiffness • skin rash or itching • unusual tiredness or weakness • stuffy or runny nose	Less common (<10% of patients): • general feeling of discomfort or illness • fever • nervousness • pain symptoms • sensitivity to heat or cold • slowed heartbeat • stomach cramps • sweating • swelling of the face, feet, or lower legs • tenderness • cough or thickening of bronchial secretions • trouble breathing, chest pain, or chest tightness • trouble sleeping • upper right abdominal or stomach pain • watery or bloody diarrhea • weight change • yellow eyes and skin
Rare (<1% of patients) • bloating • dark, bloody, or cloudy urine • blurred vision or other change in vision • darkening of the skin • dizziness • drowsiness • eye pain • fainting • fast heartbeat • indigestion • loss of appetite • mental depression • nausea or vomiting • pains in the stomach, side, or abdomen, possibly radiating to the back • redness or irritation of the eye • sensitivity of the eye to light • skin blistering, peeling, loosening, or tearing	

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8.2 Adverse Event List for SBRT

Risks and side effects related to the SBRT	
More common (>10% of patients): • Pain flair Fracture or compression of the treated bones of the spine, which can result in pain and may need surgical treatment • Fatigue • Redness of irritation of the skin in the treatment area • Hair loss in the treatment area • Some soreness of the ribs with an increased risk of rib fracture.	Less common (<10% of patients): • The following are likely with SBRT to the bones of the spine in the neck: • Inflammation of the lining of the mouth and esophagus • Inflammation of the vocal cords, leading to hoarseness or loss of voice
Rare (<1% of patients) • (radiation myelitis) Damage to the spinal cord, which can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs • Damage to the esophagus, which can cause problems with swallowing • Damage to the stomach or bowel which can lead to ulceration or perforation with a risk of infection and death. •	

8.3 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

‘Expectedness’: AEs can be ‘Unexpected’ or ‘Expected’ (see [Section 8.1-8.2](#) above) for expedited reporting purposes only.

Attribution of the AE:

Definite – The AE **is clearly related** to the study intervention.

Probable – The AE **is likely related** to the study intervention.

Possible – The AE **may be related** to the study intervention.

Unlikely – The AE **is doubtfully related** to the study intervention.

Unrelated – The AE **is clearly NOT related** to the study intervention.

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8.4 DSMC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in [Appendix D](#). DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All Adverse Events that occur during protocol intervention and are coded as either 1) **unexpected grade 4**, 2) **unplanned inpatient hospitalization $\geq$ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC 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.

8.5 WFUHS IRB AE Reporting Requirements

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

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

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

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS

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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 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in [Section 8.1](#)

9.1 Pharmaceutical Accountability

Pembrolizumab is commercially available and will be supplied in accordance with pharmacy policy and procedures.

10.0 Correlative/Special Studies

10.1 Laboratory Correlative Studies

The baseline as well as 2- and 6-month post-SBRT plasma will be tested for histamine, Calcitonin gene-related peptide (CGRP), and substance P which have compelling pre-clinical data to suggest they may be biomarkers related to pain in patients with bone metastases. Dr. Shiozawa's lab is already performing these same correlative studies in a protocol where breast cancer patients get palliative RT. This correlative analysis will be unique since SBRT results in higher rates of pain relief as well as higher rates of pain flairs. There are no biomarkers related to pain flair or pain response in the setting of spine SBRT which makes this correlative study highly novel. We plan to correlate blood histamine, CGRP, and substance P levels with pain response, pain flare, and radiographic response (improvement in thecal sac patency). Additionally, ELISA will be performed on plasma samples to characterize bone turnover markers, specifically for N-terminal propeptide of type 1 procollagen (P1NP; bone formation) and C-terminal telopeptide of type 1 collagen (CTX; bone resorption). The plasma samples will also be utilized for mass spec analysis. The whole blood collected will also be utilized for microarray analyses or next generation RNA sequencing. The changes in biomarkers between follow-up visits and baseline will be calculated. The two-sample t-tests will be used to compare changes in biomarkers between response groups at each follow-up visit. Usually, changes are normally

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distributed. If not, Wilcoxon rank sum tests will be used. For continuous pain outcomes, Spearman's rank correlation coefficients will be used to relate changes in biomarkers and pain outcomes at each follow-up visit.

11. Data Management

Form	Location of Storage
Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Current Medications Form	WISER/OnCore
Number Rating Pain Scale	RedCap
EORTC QLQ-BM22	RedCap
Survival/Withdrawal/Off Treatment/Off Study	WISER/OnCore
Follow up 30 Days	WISER/OnCore
Adverse Events	WISER/OnCore
Pretoxicity	WISER/OnCore
Vitals/ECOG	RedCap
Neurological Exam	RedCap
Thecal Sac Patency Baseline,	RedCap
Thecal Sac Patency, 2 mths, 6mths	RedCap
Correlative Data/Blood biomarkers	Will be printed on Excel Sheet by Lab and given to the Statistician
Pain Flare	RedCap

12.0 Statistical Considerations

12.1 Analysis of Primary Objective

The proportion and its 95% confidence interval for the primary outcome, the feasibility of patients completing SBRT and at least 1 cycle of pembrolizumab, will be calculated.

12.2 Analysis of Secondary Objective

Descriptive statistics will be performed for the secondary objectives at each visit. For discrete variables, the proportions and counts will be calculated for each visit. For continuous variables, means, standard deviations, medians, the first quartiles, the third quartiles, and ranges will be calculated for each visit. The 95% confidence intervals will be also estimated. Additionally, the changes in continuous outcomes (e.g., biomarkers) between follow-up visits and baseline will be calculated.

12.3 Power and Sample Size

Knowing the proportion of patients who complete treatment will be critical in allowing us to determine if subsequent trials are feasible. We estimate that 80% of patients will complete treatment. With 10 patients, the 95% confidence interval for the proportion of feasibility is estimated to be between 0.55 to 1.

12.4 Estimated Accrual Rate

We estimate we can recruit one patient every 2 months.

12.5 Estimated Study Length

In order to enroll 10 patients, it will take around 20 months. The follow-up time is 6 months. With additional 3 months for data analysis and paper writing. The estimated study length is 29 months.

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