A Trial of Palliative Lattice Stereotactic Body Radiotherapy (SBRT)

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Protocol Revision History

Initial Approval Version	**14 October 2019**
Amendment #1 Version	**04 December 2019**
Amendment #2 Version	**09 December 2019**
Amendment #3 Version	**07 February 2020**
Amendment #4 Version	**23 April 2020**
Amendment #5 Version	**15 June 2020**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Glossary of Abbreviations

AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ATC	Advanced Technology Consortium
BJH	Barnes Jewish Hospital
CBC	Complete blood count
CD4+	Cluster of differentiation 4+
CFR	Code of Federal Regulations
CMP	Comprehensive metabolic panel
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CYP3A4	Cytochrome P450 3A4
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOB	Date of birth
DSM	Data and Safety Monitoring
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FWA	Federal wide assurance
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
ICH	International Council for Harmonisation
IGRT	Image-guided radiation therapy
IMRT	Intensity modulated radiotherapy
IL	Interleukins
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
NCCN	National Cancer Center Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NRS	Numeric Rating Scale
NSCLC	Non-small cell lung cancer
OAR	Organs at risk
OHRP	Office of Human Research Protections
PD-L1	Programmed death ligand 1

PI	Principal investigator
PRO-CTCAE	Patient Reported Outcomes-Common Terminology Criteria for Adverse Events
PTV	Planning Target Volume
QASMC	Quality Assurance and Safety Monitoring Committee
QoL	Quality of Life
RNA	Ribonucleic acid
SAE	Serious adverse event
SCC	Siteman Cancer Center
SBRT	Stereotactic body radiation
SFRT	Spatially fractionated radiotherapy
Lattice SBRT	Spatially-fractionated stereotactic body radiation
SIB	Simultaneous integrated boost
SLCH	St. Louis Children's Hospital
TEAE	Treatment emergent severe adverse events
TNF	Tumor necrosis factor
TPCF	Tissue Procurement Core Facility
UPN	Unique patient number
VMAT	Volumetric modulated arc therapy
WU	Washington University

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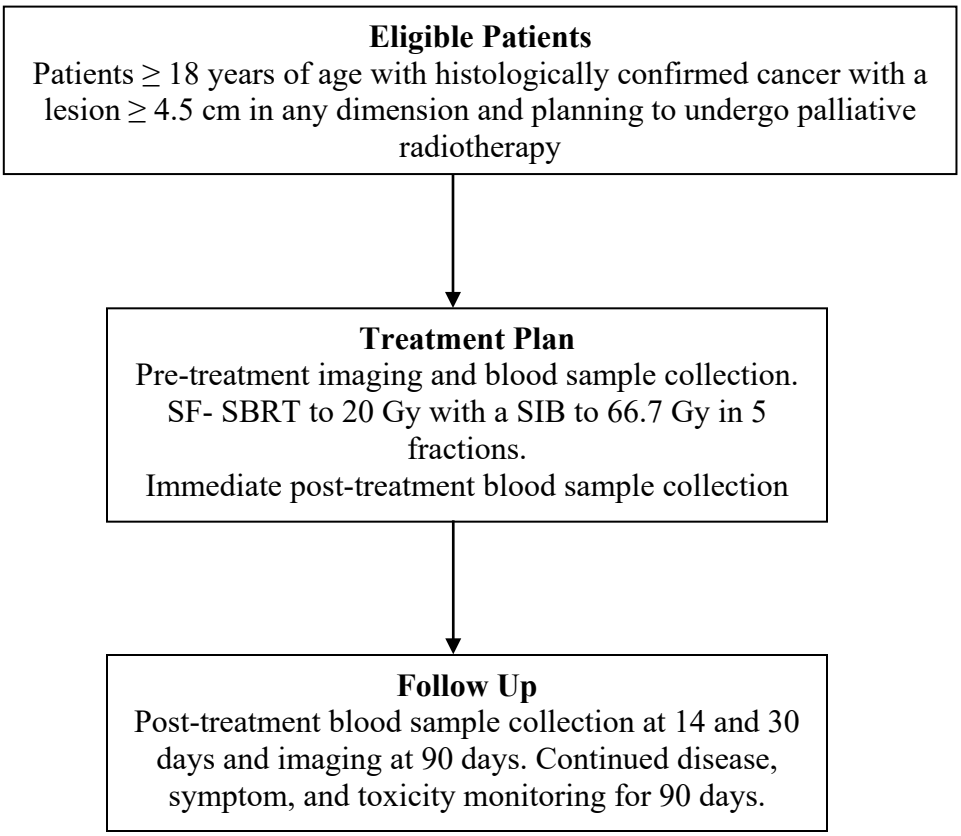
PROTOCOL SUMMARY

Synopsis

Title:	A Trial of Palliative Lattice Stereotactic Body Radiotherapy (SBRT)
Study Description:	Lattice SBRT will be used to deliver palliative radiotherapy to large (≥4.5 cm) tumors. The safety and efficacy of this approach will be assessed for this novel treatment technique.
Objectives:	**Primary Objective:** To evaluate the safety of 5-fraction palliative Lattice SBRT in patients with non-hematologic malignancies with large lesions who are planning to undergo palliative radiotherapy (≥4.5 cm). **Exploratory Objectives:** 1. To assess pain response to Lattice SBRT 2. To assess patient-reported toxicity outcomes 3. To assess patient reported quality of life outcomes 4. To evaluate blood for immune- and tumor damage-associated response with Lattice SBRT
Endpoints:	**Primary:** Rate treatment-related, non-hematologic CTCAE version 5.0 ≥ Grade 3 toxicity **Exploratory:** Pain assessment, PROMIS Global, Physical Function, Pain Interference, Anxiety, and Depression, peripheral blood immune-related biomarkers.
Study Population:	Ten patients will be enrolled, all ≥ 18 years of age with ECOG ≤ 2. All genders and races will be included.
Phase:	Unphased
Description of Sites / Facilities Enrolling:	This is a single-institutional study
Description of Study Intervention:	5-fraction Lattice SBRT delivered to 20 Gy with a simultaneous integrated boost (SIB) to 66.7 Gy.
Study Duration:	6 months plus 2 weeks for treatment and 90 days follow up
Participant Duration:	2 weeks of treatment plus 90 days follow up.

SCHEMA


Eligible Patients
Patients ≥ 18 years of age with histologically confirmed cancer with a lesion ≥ 4.5 cm in any dimension and planning to undergo palliative radiotherapy
Treatment Plan
Pre-treatment imaging and blood sample collection.
SF- SBRT to 20 Gy with a SIB to 66.7 Gy in 5 fractions.
Immediate post-treatment blood sample collection
Follow Up
Post-treatment blood sample collection at 14 and 30 days and imaging at 90 days. Continued disease, symptom, and toxicity monitoring for 90 days.

SCHEDULE OF ACTIVITIES

	Screening	Pre-Tx / Baseline	Fx 1	Fx 2	Fx 3	Fx 4	Fx 5	EOT (2 weeks post) [5]	30 Day F/U[6]	90 Day F/U[6]
Informed consent	X									
Demographics	X									
Physical exam (incl. height and weight)	X		Once during these 5 fractions[3]					X	X	X
ECOG PS	X									
Medical history	X									
Pregnancy test[4]	X									
Hematology (CBC, CMP)	X									
CT or MRI of the chest, abdomen, and pelvis		X[7]								X[8]
Peripheral blood collection		X					X	X	X	
Questionnaires		X[2]						X	X	X
Lattice SBRT[1]			X	X	X	X	X			
AE review and evaluation		X[3]----------X						X	X	X

Footnotes:

1. Treatment given every other day
2. Completed within at least 2 weeks prior to treatment
3. Every patient will be required to have 1 on-treatment visit per standard of care clinical practice
4. For women of child bearing potential only and within 20 days of study entry
5. +/- 1 week
6. +/- 2 weeks
7. Within the past 3 months
8. Within 3 months after treatment; if there's more than one scan, use the later scan

1.0 INTRODUCTION

1.1 Metastatic or Unresectable Tumors

In 2018, it is estimated that the US cancer prevalence was about 14.5 million Americans, and this is expected to balloon to approximately 19 million Americans by 2024 (American Cancer Society 2019). Metastatic or unresectable disease is the cause of cancer-related morbidity and mortality for about 90% of cancer patients (Chaffer and Weinberg 2011). Clinical presentation of disease can vary widely depending on the site of the tumor, but pain is frequently a presenting symptom (Hamilton et al. 2015).

1.2 Radiotherapy for Tumors Needing Palliation

While radiotherapy paradigms evolve, symptomatic palliation is at the forefront of treatment intent (Spencer et al. 2018; Jones and Simone II 2014). As such, appropriate modality, dose, and fractionation continue to be investigated. Ongoing studies suggest hypofractionated approaches are favorable for this population with regimens based on principles of cancer radiobiology, such as the *Spanos Regimen* and the *QUAD SHOT*, having variable success in specific disease sites (Carrascosa et al. 2007; Corry et al. 2005).

Recent data demonstrates that SBRT offers improvements over conventionally fractionated radiotherapy for palliative treatment (Sprave et al. 2018; Nguyen et al. 2019). Three issues limit the utility of SBRT. First, dose escalation can be difficult given the proximity to surrounding OARs (Hartsell et al. 2005; Shiue et al. 2018). Second, it may be unsafe to treat large tumors with SBRT. Retrospective data and secondary analyses from SBRT trials for NSCLC suggest that 5 cm should be the upper limit for which SBRT may be employed (Allibhai et al. 2013; Videtic et al. 2017). Third, SBRT may not be as effective for larger lesions as it is for smaller lesions. Prior studies support this limitation. (Ricco et al. 2017; Masucci 2018)

1.3 Spatially Fractionated Radiotherapy (SFRT)

SFRT may address these limitations of traditional SBRT. SFRT relies on beam collimation to create high-dose "peaks," organized throughout a target volume with intervening low-dose "valleys" (Billena and Khan 2019). SFRT as a 2-dimensional technique is being evaluated in soft tissue sarcoma in a prospective setting (M. Mohiuddin et al. 2009; Mohammed Mohiuddin et al. 2014). In these studies, a single dose of 2-dimensional SFRT was used either alone or in combination with further conventionally fractionated radiation with or without chemotherapy with1-2 year LC greater than 90% and limited Grade 2-3 skin toxicities.

Lattice radiotherapy is a form of SFRT that uses a 3-dimensional beam arrangement to target high-dose spherical volumes which allows for a more flexible beam arrangement, better normal tissue optimization, and lower exit beam skin dose (X et al. 2010). Classically, SFRT had been planned to achieve a dose fall off to 20-30% of the "peak"

dose (Meigooni et al. 2006). Tested approaches for Lattice designate spheres 1-2 cm spaced 2-3 cm apart (center to center) (Amendola et al. 2018; E et al. 2010). Prior studies show that Lattice SFRT can be delivered using IMRT or VMAT (Gholami et al. 2016; Billena and Khan 2019).

1.4 Correlative Studies Background

In animal models, extreme hypo-fractionation was found to induce infiltration of T-cells (Lugade et al. 2005). Also, SBRT has been shown to alter levels of soluble PD-L1, IFN α/β/γ, TNFα, and various interleukins (Trovo et al. 2016; Ellsworth et al. 2017; Walle et al. 2018; Song et al. 2019).

It is hypothesized that SFRT spares interspersed small volumes of normal tissue allowing it to tolerate higher doses of radiotherapy while immune-mediated bystander effects allow for cell kill of areas of tumor receiving a lower dose. This hypothesis is supported by the finding SFRT is associated with increased serum TNFα and that higher levels of TNFα are associated with complete tumor response (Sathishkumar et al. 2002).

SFRT has been shown to elicit a local effect by the "bystander effect" (i.e. effects to tumor cells in the valleys) via secretion of cytokines, induction of cellular repair pathways, and induction of apoptosis (Sathishkumar et al. 2016; Najafi et al. 2014; Asur et al. 2012).

While SBRT and SFRT are both felt to elicit robust immune responses, the immunogenic effects of Lattice SBRT have not been studied.

1.5 Rationale for treatment approach

Standard palliative radiotherapy regimens may provide limited durability of response in large tumors. Thus, there is a clinical need for a new approach. A standard palliative radiotherapy regimen is 20 Gy in 5 fractions, and therefore it is reasonable to assume that this should be the minimum dose delivered for adequate tumor coverage in an Lattice SBRT plan. Assuming that this represents the 30% isodose (i.e. the "valley"), this would allow appropriate dose escalation in the "peak" to 66.7 Gy (i.e. the 100% isodose). The Lattice SBRT approach may improve symptom response, LC, and better prime the tumor microenvironment for immune response (Ko, Benjamin, and Formenti 2018; Walle et al. 2018; Krombach et al. 2019) compared with canonical palliative radiotherapy doses with the added benefit of less toxicity than a traditional homogenous SBRT plan.

1.6 Study Design

1.6.1 Overall Design

This is a study evaluating the safety of Lattice SBRT for patients with large tumors (≥ 4.5 cm) planning to undergo palliative radiotherapy. Eligible patients will undergo radiotherapy using Lattice SBRT. Lattice SBRT will be prescribed

to 20 Gy in 5 fractions delivered every other day with a Lattice SIB to 66.7 Gy in 5 fractions. Patients will be followed for 90 days after the completion of all therapy for treatment-related toxicity assessment.

An exploratory study will analyze blood-based markers of treatment response, so blood will be drawn prior to and after completion of radiotherapy.

1.6.2 Scientific Rationale for Study Design

Tumor burden incurs significant morbidity in terms of symptomatology, including pain, dyspnea, hemoptysis, and mass effect on surrounding organs. Palliative hypofractionated radiotherapy is known to be a useful modality for control and/or amelioration of such symptoms. However, large tumors are difficult to treat with traditional palliative methods. Hypofractionated radiotherapy may offer insufficient control and SBRT may be associated with a high rate of toxicity.

Dose escalation using SFRT my offer improved local control, symptom relief, and reduced toxicity compared with traditional radiotherapy methods. Also, SFRT has been associated with significant activation of systemic anti-tumor cytokines and chemokines. Since Lattice SBRT has not been tested, the goal of this study is to evaluate the safety of this approach.

1.6.3 Justification for Dose

One standard regimen for palliative radiotherapy is 20 Gy in 5 fractions. In SFRT, the traditional dose gradient between minimum tumor dose and maximum tumor dose is 30% to 100%, respectively. Using 20 Gy in 5 fractions as traditional coverage for lesions needing palliation (i.e. 30% “valley” tumor coverage), the “peak” 100% dose is 66.7 Gy in 5 fractions.

1.7 Risk/Benefit Assessment

1.7.1 Known Potential Risks

High-dose radiation has been known to cause toxicity to normal tissue. This is manifested variably depending on the area of the body treated. While the potential toxicities can be serious and include death, these toxicities are rare when high-quality, high-dose radiation is delivered within established normal tissue dose constraints using appropriate immobilization, image guidance, and institutional experience. We have successfully tested many Lattice SBRT plans prescribed to 66.7 Gy in 5 fractions using institutional quality assurance protocols similar to conventional SBRT. Therefore, we expect the toxicity risks associated with Lattice SBRT plans to be similar to conventional SBRT if the required established dose constraints are met.

Blood collection prior to and after radiotherapy poses a small risk of pain and bleeding.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
To evaluate the safety of palliative Lattice SBRT in patients with non-hematologic malignancies with large lesions in need of palliative radiotherapy (≥ 4.5 cm)	Rate treatment-related, non-hematologic CTCAE v5.0 Grade ≥ 3 toxicity	SBRT to large tumors is traditionally associated with high dose to OARs, with sequelae of radiation-induced toxicities. As these patients have no effective treatment options, evaluation of the safety of this method of dose-escalation with SBRT is warranted. CTCAE v5.0 is a widely accepted standardized measure of treatment-related toxicity.
Exploratory		
To assess pain response to Lattice SBRT	For patients that have pain, their pain level will be assessed with the pain Numeric Rating Scale (NRS)	The NRS is an 11-point scale for patient self-reporting of pain. This is selected because it is a reliable and clinically meaningful measure of pain that is extensively used in research and clinical practice.
To assess patient-reported toxicity outcomes	For patients that do not have pain, patient-reported symptom response will be assessed with PRO-CTCAE	PRO-CTCAE is a standardized inventory to collected patient reported symptomatic adverse events in clinical trials.
To assess patient reported quality of life outcomes	Patient reported quality of life and functional outcomes will be measured before treatment, after treatment, and at each follow up with the PROMIS Global, Physical Function, Pain Interference, Anxiety, and Depression system	This patient reported outcome inventory was selected because it is a reliable and clinically meaningful measure of patient reported toxicities and functional outcomes.
To evaluate blood for immune- and tumor damage-associated response with Lattice SBRT	Whole blood will be collected at baseline and after Lattice SBRT for exploratory studies of immune and tumor damage associated-response	The response of immune-related markers will be assessed before and after Lattice SBRT to better understand the immunogenic effects of treatment on tumor.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed cancer.

2. Planning to undergo palliative radiotherapy to a lesion ≥ 4.5 cm as measured with radiographic imaging or with calipers by clinical exam.

3. ECOG performance status ≤ 2

4. At least 18 years of age.

5. Radiotherapy is known to be teratogenic. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of the study, and 6 months after completion of the study

6. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Prior radiotherapy that overlaps with any planned site of protocol radiotherapy.

2. Patients with tumors in need of urgent surgical intervention, such as life-threatening bleeding or those at high risk for pathologic fracture.

3. Currently receiving any cytotoxic cancer therapy regimens or VEGF inhibitors that will overlap with the Lattice SBRT administration.
   a. Cytotoxic chemotherapy and VEGF inhibitors prior to radiotherapy or planned after radiotherapy delivery are allowed at the discretion of the treating radiation oncologist. This includes continuing a treatment plan which was initiated prior to the start of radiotherapy. A 2 week washout is recommended, but not required.

4. Pregnant. Women of childbearing potential must have a negative pregnancy test within 20 days of study entry.

5. Patients with HIV are eligible unless their CD4+ T-cell counts are < 350 cells/mcL or they have a history of AIDS-defining opportunistic infection within the 12 months prior to registration. Concurrent treatment with effective ART according to DHHS treatment guidelines is recommended. Recommend exclusion of specific ART agents

based on predicted drug-drug interactions (i.e. for sensitive CYP3A4 substrates, concurrent strong CYP3A4 inhibitors (ritonavir and cobicistat) or inducers (efavirenz) should be contraindicated).

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. The registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated

Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Strategies for Recruitment and Retention

Our institution sees a high volume of patients that are referred for palliative radiotherapy.

The primary source of patients who are eligible for this study will be radiation oncologists within our department. The most likely service lines to see patients with large tumors in need of palliative radiotherapy are sarcoma, thorax (i.e. lung cancer), gastrointestinal, gynecologic, palliative, and head and neck. Dr. Spraker (service line chief of sarcoma) is the PI, and the other service line chiefs are enthusiastic about this trial and are listed as co-investigators: Dr. Clifford Robinson (Thorax), Dr. Hyun Kim (Gastrointestinal), Dr. Perry Grigsby (Gynecologic), Dr. Chris Abraham (Palliative), and Dr. Wade Thorstad (Head and Neck). Additionally, a full-time research coordinator will be assigned to this study who will be screening all patients who are referred to our department for palliative radiotherapy.

With the current rate of patients in need of palliative radiotherapy presenting to our department, we anticipate approximately 125 patients per year will be eligible for this protocol. A conservative estimate is that 20% of these patients will consent to participate in this study. This yields an estimated accrual of 25 patients per year. We anticipate that we will enroll 10 patients of all genders, races, and ethnicities. Given the hypofractionated course of therapy, 90% of patients should be able to complete therapy. We anticipate that we will accrue approximately 1-2 patients per month, therefore completing accrual in 6 months. Patients will be accrued from the outpatient clinics and inpatient hospitals of one U.S. site. Potential participants will be identified by our multidisciplinary team physicians and discussed in tumor board.

5.0 TREATMENT PLAN

5.1 Study Intervention Description

Consenting and eligible patients will undergo Lattice SBRT prescribed to a dose of 20 Gy in 5 fractions with a simultaneous integrated boost of 66.7 Gy in 5 fractions. As long as radiotherapy fields do not overlap, treatment of up to 4 other tumor sites are allowed. Lattice SBRT is required for all tumor sites $\geq$ 4.5 cm. Lattice SBRT fractions will be delivered every other day. For sites < 4.5 cm, other planning techniques may be used (i.e. 3D conformal or SBRT). Following radiotherapy, patients will be evaluated for toxicity at 14, 30, and 90 days.

Peripheral blood will be collected from patients before treatment, immediately after radiotherapy completion (Fraction 5), within 7-14 days after radiotherapy, and 30 days after radiotherapy.

5.2 Pre-Radiation Evaluation

- History and physical exam by team radiation oncologist
- CBC & CMP
- CT or MRI of the chest, abdomen, and pelvis
- Completion of baseline NRS pain score (if applicable), PRO-CTCAE (if applicable), PROMIS Global, Physical Function, Pain Interference, Anxiety, and Depression questionnaires
- Peripheral blood collection.

5.3 Radiation Therapy

Lattice SBRT must be used for at least one lesion 4.5 cm or greater. The prescription dose for Lattice SBRT is 20 Gy in 5 fractions with a SIB to 66.7 Gy in 5 fractions. For Lattice SBRT, patients must be treated with intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT).

For Lattice SBRT, each lesion should be treated no more frequently than every other day, but treatment of each lesion may be staggered so that the patient has radiotherapy daily. No more than 3 lesions should be treated on the same day.

For other lesions, a standard palliative regimen of 5 fractions or less is encouraged but not required.

Multiple Lattice radiotherapy plans delivered during the trial period may not overlap. Reirradiation of prior irradiated sites is not allowed.

5.3.1 Localization, Simulation, and Immobilization

Simulation and treatment position will be determined by the treating radiation oncologist and team. Patients should be optimally positioned for stereotactic body radiation therapy with alpha cradles, aquaplast masks, or other methods of immobilization. The use of devices to alter dose distributions, such as bolus or lead shields, are allowed. Use of techniques to control and/or accommodate tumor motion may also be employed in constructing the planning target volume (PTV).

A treatment planning CT scan or MRI in the treatment position will be required to define the PTV. The extent of the CT scan will be determined at the discretion of the treating physician. A CT scan slice thickness of ≤ 5 mm should be employed.

5.3.2 Treatment Planning/Target Volumes

The definitions for the GTV, PTV and normal structures used in this protocol generally conform to the 1993 ICRU report #50 titled Prescribing, Recording and Reporting Photon Beam Therapy.

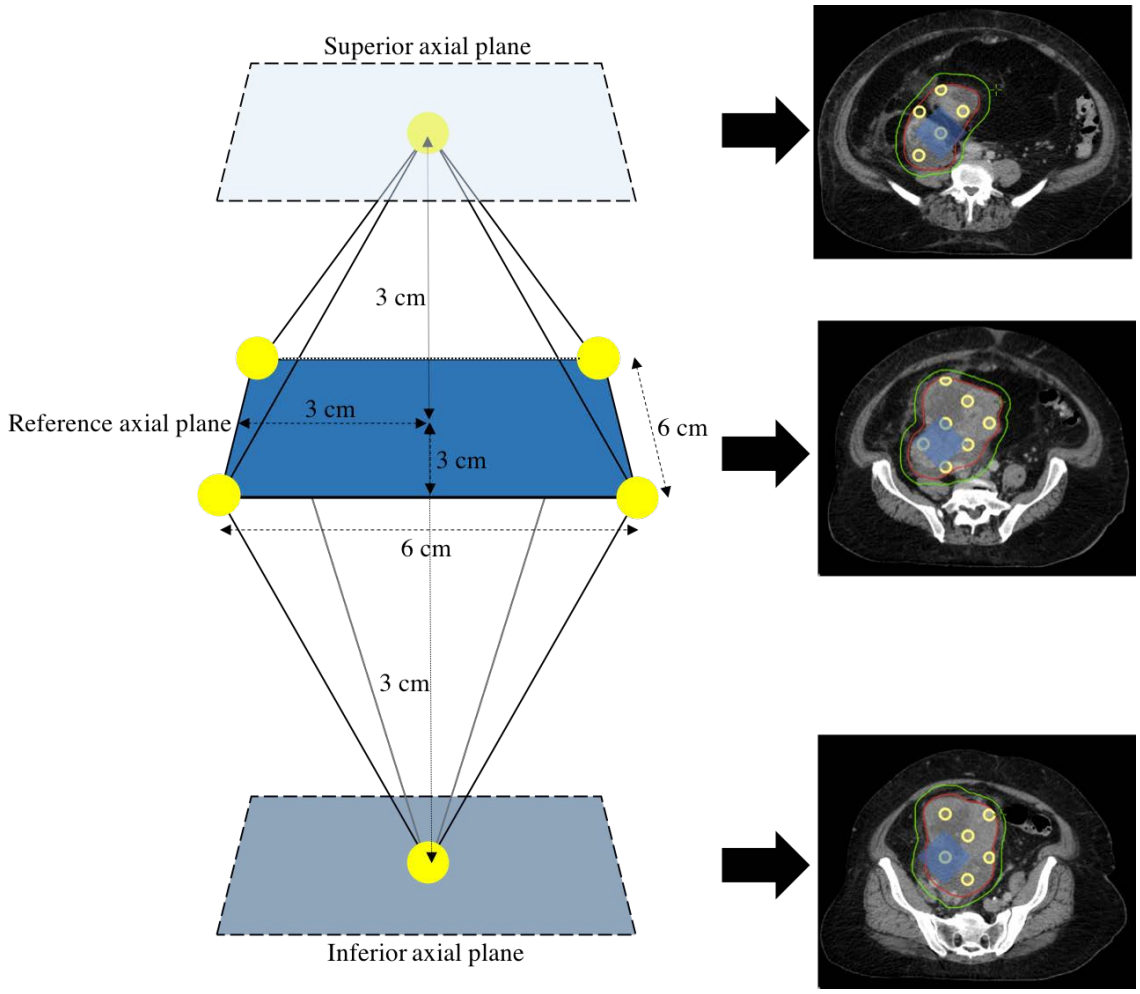
5.3.2.1 Target Volumes and Normal Structures

Target Volumes

Gross Tumor Volume (GTV): Contour using all available clinical and radiographic information. Fusion of other diagnostic imaging to delineate the GTV is allowed. Construction of an iGTV using 4DCT imaging is allowed. For boney lesions of the spine, the entire involved vertebral body may be included in the GTV.

Planning Target Volume 2000 cGy (PTV_2000): Represents a geometric expansion of the GTV (or iGTV) of up to 1.0 cm. The PTV should be reduced as not to extend beyond the patient (i.e. in to air) and may be reduced as to not extend into skin (i.e. external contour contracted by 3-5 mm).

Planning Target Volume 6670 cGy (PTV_6670): Spheres with diameter 1.5 cm should be placed 6 cm apart as measured from center to center inside the GTV. The spheres should be placed to maximize the number of whole spheres within the GTV. There should be 3 cm between axial slices in which spheres are placed. Vertices will be offset such as to create an octahedron between 3 slices on which spheres are placed. See the figure below for a geometric explanation. Crop all sphere volume extending outside of the GTV.



Geometric representation of sphere placement. Yellow dots represent the center of each sphere. Short dashes represent in-plane distances, dotted lines represent out-of-plane distances. Note that superior/inferior axial planes have spheres offset by 3 cm in-plane. To the right are axial slices representing yellow sphere placement in each plane. A blue diamond is represented to indicate vertices in the reference axial plane, and the center of vertices in planes 3 cm superior and inferior to this.

Normal structures: Relevant normal structures and their dose constraints are described in the table below. Each normal structure should be contoured in its entirety.

5.3.2.2 Radiation Treatment Planning

CT-based planning with tissue inhomogeneity correction is required. Daily IGRT is required. Motion management strategies such as breath holding, respiratory gating, fluoroscopy, and MR-guided daily adaptive therapy are allowed.

5.3.2.3 Planning Objectives and Normal Tissue Constraints

The normal tissues in the table below are to be contoured in their entirety when present on the CT simulation scan.

The following organs and doses are guidelines for the radiation treatment plan. **Organ at risk tolerance levels cannot be exceeded.** Under coverage of PTV targets in order to meet OAR constraints is allowed.

- PTV_2000: at least 95% should be covered by 20 Gy. Keeping D_{max} within the PTV_2000 and outside the PTV_6670 to less than 24 Gy is recommended but not required.
- PTV_6670: at least 95% should be covered by 66.7 Gy. A D_{min} of at least 60 Gy within vPTV is recommended.

Serial Tissue	**Max point* dose (Gy)**
Optic pathway	25
Cochlea	22
Brainstem (excluding medulla)	31
Spinal cord and medulla	28
Cauda equina	31.5
Sacral plexus	32
Esophagus	35
Brachial plexus	32.5
Heart/pericardium	38
Great vessels	53
Trachea and large bronchus	40
Bronchi	33
Skin	38.5
Stomach	35
Bile duct	41
Duodenum	26
Jejunum/ileum	32
Colon	40
Rectum	55
Ureter	45
Bladder wall	38

*A point is defined as volume ≤ 0.035 cc)

Parallel Tissue	**Critical Dose (Gy)**	**Critical Volume**
Lungs - GTV	12.5	< 1500 cc
	13.5	< 1000 cc
		< 37%
Liver	21	< 700 cc

Renal cortex (bilateral)	28	< 200 cc
Femoral Heads (Right & Left)	30	<10 cc

5.3.3 Dose Specifications

For Lattice SBRT, the daily prescription dose will be 20 Gy to be delivered to the PTV_2000 with a SIB of 66.7 Gy to be delivered to the PTV_6670 over 5 fractions (4 Gy and 13.34 Gy to the PTV_2000 and PTV_6670 per day, respectively). All doses will be prescribed to the periphery of the PTVs. In general, the prescription isodose line (generally 93-98%) chosen should encompass at least 95% of the PTV. Under coverage of the PTV to meet dose constraints is allowed.

The maximum point dose, minimum point dose, and the mean dose to the PTV will also be reported.

5.3.4 Technical Factors

The guidelines for VMAT in this trial will conform to the policies set by the Advanced Technology Consortium (ATC) and the National Cancer Institute (NCI). Each of the target volumes and normal structures listed below must be delineated on each slice from the 3D planning CT in which that structure exists.

5.3.5 Radiation Quality Assurance

Radiation quality assurance will be evaluated by a Medical Physics team. Prior to treatment, plan quality will be assessed with an ion chamber and film-based dosimeters.

5.4 Patient-Reported Quality of Life Outcome and Toxicity Measures

Symptom response and patient-reported quality of life will be measured using the pain numeric rating scale, PRO-CTCAE (abridged as indicated in Appendix D), PROMIS Global, Physical Function, Pain Interference, Anxiety, and Depression questionnaire at the following time points:

1. Within 2 weeks prior to the start of radiotherapy
2. Within 2 weeks after completion of radiotherapy
3. At 30 days after radiotherapy
4. At 90 days after radiotherapy

The patient reported outcomes measures will be conducted using a computer-assisted interview program and may be done in person before/after a routine office visit or over the phone at the preference of the study participant. Patient reported outcomes may also be collected online.

5.5 Acquisition of Blood for Research

Refer to Section 8.0.

5.6 Definitions of Evaluability

All patients enrolled on the study are evaluable for toxicity if they have received at least one fraction of radiation. Patients are evaluated from first receiving study treatment until 90 days after the conclusion of treatment or death.

5.7 Concomitant Therapy and Supportive Care Guidelines

Patients may not receive any concurrent cytotoxic chemotherapy or VEGF inhibitors with radiation. The interval from last receipt of cytotoxic chemotherapy or VEGF inhibitors to the initiation (or re-initiation) of subsequent therapy will be at physician discretion. Supportive care will be consistent with standards for palliative radiotherapy, directed by the treating physician.

5.8 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum/urine pregnancy test within 20 days prior to the first dose of radiation.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 6 months following the last dose of radiation.

If a patient is suspected to be pregnant, radiation should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume therapy.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 6 months after the last dose of radiation, the investigator must be notified in order to facilitate outcome follow-up.

5.9 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for a maximum of 2 weeks or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.10 Follow-up Specifications

5.10.1 Duration of Follow Up

Patients will be followed at 14, 30, and 90 days after completion of radiotherapy. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients may be followed in-person during visits, medical records review, phone calls, office visits, and assessment of any other clinically relevant materials after completion of therapy.

5.11 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 4 weeks and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 1-2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 RADIATION THERAPY DOSE/DELAYS MODIFICATIONS

The planned course of radiation therapy is five fractions delivered every other day to each lesion. For plans unable to meet dose constraints to OARs, under coverage of the PTV in order to meet the constraints is recommended. Patients with delayed treatment starts of any duration may be treated using existing or new plans at physician discretion. Continuance of treatment for delays while on-treatment will be at the discretion of the treating physician.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 90 days following the completion of radiotherapy. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- AEs that do not fall under the following categories
    - Gastrointestinal
    - Hepatobiliary
    - Immune system
    - Metabolic
    - Nervous system
    - Renal and urinary
    - Respiratory
    - Skin disorders
- AEs that are grade 1

Refer to the data submission schedule in Section 9.0 for instructions on the collection of AEs in the EDC.

7.1 WU PI Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 CORRELATIVE STUDIES

8.1 Blood Sample Collection and Processing

Patients will be have up to 50 mL of anticoagulated blood collected in up to 5 EDTA purple top tubes at the following time points:

- Baseline
- immediately after radiotherapy completion (Fraction 5)
- 14 days after radiotherapy
- 30-days follow-up

All samples will be marked with the patient's study number, initials, and date of sampling with the use of an indelible marker.

Blood and tissue samples will be stored in Dr. Aadel Chaudhuri's lab in the Cancer Biology Division of the Department of Radiation Oncology.

8.1.1 Plasma and Whole Blood

Each sample will be labeled with a unique de-identified specimen ID number, and stored in Dr. Chaudhuri's lab until analysis. Specifically, blood samples (up to 50 mL) will be collected in 5 EDTA (10 mL each) purple top tubes at baseline, post-

treatment (i.e. immediately following fraction 5), 14 days after treatment, and at 30 days follow-up. EDTA whole blood samples will be spun at 1200 g and processed for platelet depleted plasma and peripheral white blood cells. Nucleated white blood cells will be isolated using Ficoll or Lymphoprep extraction using Sepmate tubes, washed in phosphate buffered saline, then divided into approximately 10 x 10^6 cells/aliquot, and cryopreserved at -80° C for 24-72 hours, then moved for longer term storage in a LN_2 tank. All plasma and aliquots of platelet-depleted whole blood will also be stored at -80° C.

All samples should be sent to:

Aadel Chaudhuri, M.D., Ph.D.
Peter Harris, Ph.D. (Lab Manager)
4511 Forest Park Avenue
Phone: 314-273-9040, 269-598-2212 (cell)

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Specimen Collection Form	Screening, immediately after radiotherapy completion (Fraction 5), 14 days after radiotherapy, and 30 days after radiotherapy
Questionnaires	Baseline, after radiation at 2 weeks, 1 month, and 3 months
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	After radiation at 2 weeks, 1 month, and 3 months
Death Form	At time of death (if applicable)

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy (phase I studies only if efficacy is objective of the protocol)
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a single arm study where *20* eligible patients with non-hematologic malignancies patients with large tumors (≥ 4.5 cm) will undergo radiotherapy using Lattice SBRT. Lattice SBRT will be prescribed to 20 Gy in 5 fractions delivered every other day with a LATTICE simultaneous integrated boost (SIB) to 66.7 Gy in 5 fractions. Patients will be

followed for 90 days after the completion of all therapy for treatment-related toxicity assessment. An exploratory study will analyze blood-based markers of treatment response, so blood will be drawn prior to and after completion of radiotherapy.

11.2 Study Endpoints

The primary endpoint is treatment related severe adverse event rate defined as the percentage of patients with grade 3 or higher non-hematological toxicities as scored by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.

The exploratory endpoints include blood-based markers of treatment response, pain response to Lattice SBRT, patient reported quality of life (QoL) outcomes using the in-field response, PROMIS Global, Physical Function, Pain Interference, Anxiety, and Depression questionnaire, before and after treatment with Lattice SBRT.

11.3 Data Analysis

Demographic and clinical characteristics will be summarized using descriptive statistics. Paired t-test and/or paired-sample Wilcoxon Signed Rank test will be used to compare the QoL scores between before and after treatment with Lattice SBRT.

11.4 Power Analysis and Sample Size

Approximately 20 evaluable patients will be enrolled. The proposed sample size was chosen to allow assessment of safety. With an expected ≥ grade 3 non-hematological toxicity rate around 30%, there is a 99.53% probability of observing at least one toxicities in the 20 patients.

11.5 Accrual

The rate of accrual for the study is expected to be about 1 patient per month. It is estimated 20 eligible patients will be enrolled in 10-12 months.

11.6 Continuous Toxicity Monitoring using Pocock-type boundary

The toxicities will be reviewed and monitored on a continuous basis. Early stopping of this trial will be based on the excessive Lattice SBRT treatment emergent severe adverse events (TEAE) of grade 3 or higher non-hematological rate. We assume the TEAE rate is expected ~30% and a toxicity rate of 40% or more is not desired. Sequential boundaries will be used to monitor dose-limiting toxicity rate after three patients are enrolled and evaluable for toxicity. The accrual will be halted if excessive numbers of TEAE are seen, that is, if the number of TEAE is equal to or exceeds bn out of n patients with full follow-up (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.3 when the rate of TEAE is equal to the acceptable rate of 0.3 (Ivanova, Qaqish, and Schell 2005).

number of patients	4	5	6	7	8	9	10	11	12	13	14	15

Boundary (bn)	4	5	5	6	6	6	7	7	8	8	9	9

Thus, based on the continuous monitoring algorithm for toxicity using Pocock-type boundary, the study will halt if excessive Lattice SBRT -related adverse events occur in the 4 of the first 4 patients, or 6 of the first 8, or 7 of the first 11, or 9 of the 20 patients has completed the trial.

The operating characteristics including early stopping probability, expected number of TEAEs and associated with the calculated boundaries are listed below.

TEAE rate	*Early stopping (hitting the boundary) probability*	*Expected number of TEAEs*	*Standard deviation on number of TEAEs*	*Expected number of patients enrolled*	*Standard deviation of number of patinets enrolled*	*Expected TEAE rate*	*Standard deviation on TEAE rate*
0.30	0.0447	4.41	1.65	14.71	1.50	0.31	0.15
0.40	0.1707	5.58	1.54	13.96	2.65	0.43	0.18
0.50	0.4101	6.24	1.38	12.49	3.67	0.55	0.19
0.60	0.6957	6.24	1.40	10.40	4.06	0.67	0.18
0.70	0.9052	5.72	1.38	8.18	3.61	0.77	0.16
0.80	0.9878	5.05	1.11	6.31	2.60	0.85	0.14
0.90	0.9998	4.46	0.72	4.96	1.53	0.93	0.10
1.00	1.0000	4.00	0.00	4.00	0.00	1.00	0.00

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Serious AND unexpected suspected adverse reaction		
Unexpected fatal or life-threatening suspected adverse reaction		
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
		every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

APPENDIX D: PRO-CTCAE Inventories

All patients will complete the following PRO-CTCAE inventories:

- Rash
- Numbness/tingling
- Dizziness
- Concentration
- Memory
- General pain
- Fatigue
- Insomnia
- Anxious
- Discouraged
- Sad

Patients with GI cancers (including esophagus, lower GI, and retroperitoneal sarcoma) will complete the following additional PRO-CTCAE inventories:

- Decreased appetite
- Nausea
- Vomiting
- Heartburn
- Gas
- Bloating
- Hiccups
- Constipation
- Diarrhea
- Abdominal pain
- Fecal incontinence

Patients with thoracic cancers (including esophagus, lung, and chest wall) will complete the following additional PRO-CTCAE inventories:

- Decreased appetite
- Nausea
- Vomiting
- Heartburn
- Gas
- Bloating
- Hiccups
- Shortness of breath
- Wheezing
- Voice changes
- Hoarseness

Patients with pelvic cancers (including prostate, gynecologic, sarcomas, rectum, anus) will complete the following additional PRO-CTCAE inventories:

- Vaginal discharge
- Vaginal dryness
- Painful urination
- Urinary urgency
- Urinary frequency
- Change in urine color
- Urinary incontinence
- Erection
- Ejaculation
- Libido
- Delayed orgasm
- Unable to have orgasm
- Pain with intercourse

Patients with head and neck cancers will complete the following additional PRO-CTCAE inventories:

- Dry mouth
- Swallowing
- Mouth sores
- Cheilitis
- Voice changes
- Hoarseness