Clinical Investigational Plan (CIP)

Feasibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01)

Protocol Number VAR-2019-02
NCT 04592887

Version 08
April 29, 2021

Sponsor and Monitor:

Varian Medical Systems
3100 Hansen Way
Palo Alto, CA 94304 USA

Summary of Changes from Previous Version:

Version	Affected Section(s)	Summary of Revisions Made	Rationale
08	2.7	Removed exclusion criteria "Patients with a diagnosis of hematological malignancy"	The criterion changed to improve the recruitment rate while maintaining study goals.
07	Title page, 2.83, 2.9, 5	Updated study short name from "FAST BONE" to "FAST-01"; Updated dosimetric constraints; Updated sponsor contact information for adverse event reporting and monitoring	Study short name revision, dosimetric constraints updated as per feedback from site; sponsor contact information revision
06	2.7, 2.8.2, 3.1; 2.13; 3.1; Title	Updated exclusion criteria to include pregnancy with corresponding additions to the	Updated per feedback from Radiation Safety Committee review; Revision for clarity

	page, 2.1, 2.8.5 & 2.8.6, 2.14, 9	other sections indicated; Updated Stopping Rule to include major device malfunction; Updated potential risks; Addition of study name "FAST-Bone" to the study title, Added the information for the single institutional study site; Added the term "baseline", Updated data collection list to include photographs (skin), Added Chair and Vice Chair designations	
05	2.2.2, 2.8.7, 2.8.8; 3.1	Updated to allow for remote visits at all post-treatment follow-up visit time points; included additional tissues under potential risks	Update per feedback from FDA review
04	1.3; 2.2.1; 2.2.2; 2.4; 2.6; 2.7; 2.8.3; 2.8.6; 2.8.7; 2.13; 7; 9, 10; 2.3, 2.7 – 2.16, 3, 4, 5, 7	Updated duration of investigation; Updated protocol summary; Revised Schedule of Activities table; Combined primary and secondary objectives assessing skin and other toxicities into one primary objective to assess toxicities of treatment, added use of pain medication and removed QOL from secondary objective; Changed follow-up end point to death or lost to follow-up; Revised pre-defined field sizes to larger field sizes, lesions of the feet, hands, wrists excluded, diagnosis of hematological malignancy or patients at known risk of enhanced normal tissue radiosensitivity excluded, pacemakers or other implanted devices excluded; Included additional description of pre-defined field sizes and isodose line coverage; Included patient questionnaire for assessing flare in bone pain; Included description of follow-up time points and activities; Revised analyses for objective measures, revised stopping rules, sample size; Added text for IUO label; Removed reference to additional investigational sites; Changed section headings to numerical numbering	Update based on revisions to the protocol; To correspond with revisions to the protocol; Provide additional details for the schedule of study activities and incorporate the revisions to the protocol; Assess all toxicities and not only skin toxicity, follow published methodology for pain assessment; Follow subjects for a longer time period to assess toxicity; Accommodate treatment sites, reduce potential for debilitating injury, exclude conditions that may result in higher radiosensitivity, potential for malfunction due to neutron production; Provide additional information on PTV and dose; Follow published methodology for pain assessment; Provide description in addition to Schedule of Activities of table; Assess all toxicities and not only skin toxicity, following published methodology for pain assessment; Text is being provided in the CIP and not separately; Study will be carried out at 1 investigational site; Revision for clarity; Reference sections specifically
03	IV E 2,3,5	Added text that a subject may have up to 3 bone metastases treated	Scientific review committee feedback

02	I, III A-C, IV C-F, IV J, V A, V C, X	Title text “painful” changed to “symptomatic”; metastasis(-es) in pelvis removed; skin toxicity assessment added to primary objective; inclusion criteria minimum age changed to 18 years; clarification added for assessment of inclusion criterion; added lesion size, CTV, PTV; listed clinical centers for follow-up visits; details added for AE evaluation and management, and primary objective analyses; stopping rule threshold changed to at least three subjects; updated risks and mitigation; updated device description	Scientific review committee feedback; clarifications
01	N/A	N/A	New document

Table of Contents

1 Purpose

1.1 Name and Intended Use of the Device

Name:
FLASH enabled ProBeam Proton Therapy System

Intended use of the FDA cleared ProBeam Proton Therapy System (510(k) K133191):
ProBeam Proton Therapy System provides protons for precision radiotherapy of lesions, tumors, and conditions anywhere in the body where radiation treatment is indicated.

Intended use of the investigational device for this clinical study:
The FLASH enabled ProBeam Proton Therapy System is intended to deliver FLASH radiotherapy to patients with painful bone metastases in extremities.

1.2 Objectives of the Investigation

The objectives of this investigation are to assess the workflow feasibility of FLASH radiotherapy in a clinical setting, toxicities, and pain relief at the treated site(s) following treatment of painful bone metastasis(-es) in extremities.

1.3 Duration of the Investigation

Enrollment for the study is expected to take 12 months.

Subjects will be on study prior to their radiation treatment simulation (approximately 1-2 weeks), during their radiation treatment simulation, plan selection, and delivery (≤ 7 business days), and during post-treatment follow-up (until subject death or lost to follow-up). In general, subjects with metastatic disease have a guarded prognosis. Their survival varies with their diagnosis and rate of disease progression. Thus, it is not possible to specify the duration of a subject's participation in the study. Subject participation may last from a few months to several years.

The study may run from 1.5 years to several years (which covers enrollment, treatment, follow-up, and completion of data analyses).

2 Protocol

2.1 Protocol Signature Page

Feasibility study of FLASH radiotherapy for the treatment of symptomatic bone metastases

Protocol Number VAR-2019-02

Version 08
April 29, 2021

I have read and understood this clinical investigational plan and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will ensure they are fully informed regarding the investigational device and the conduct of the study according to US FDA Good Clinical Practices, applicable state and local regulations, and Institutional Review Board (IRB) requirements. I agree to collect and report all study data according to this clinical investigational plan.

Cincinnati Children's Hospital Medical Center	
Investigational Site	
John C. Breneman, MD	Cincinnati, OH
Principal Clinical Investigator – Print Name	**Location (city, state)**
Principal Clinical Investigator Signature	**Date**
Dr Ricky Sharma, MD PhD, Vice President Clinical Affairs	Palo Alto, CA
Sponsor Representative – Print Name and Title	**Location (city, state)**
Sponsor Representative Signature	**Date**

2.2 Protocol Summary

2.2.1 Protocol Synopsis

Study Title	Feasibility study of FLASH radiotherapy for the treatment of symptomatic bone metastases
Study Description	This clinical study is designed as a prospective feasibility study to assess the workflow feasibility of FLASH radiotherapy in a clinical setting, toxicities, and pain relief following treatment of painful bone metastasis(-es) in the extremities.
Objectives	Primary Objective: 1. Assess workflow feasibility of FLASH radiotherapy in a clinical setting 2. Assess toxicities of treatment Secondary Objective: 3. Assess pain relief at the treated site(s)
Outcome Measures	Primary Objective Outcome Measure: 1. **Workflow feasibility:** • Patient time on the treatment table • Delays in study treatment related to the investigational device (excluding delays due to patient or facility factors not related to study treatment) 2. **Toxicities of treatment:** • Toxicities that are possibly, probably, or definitely related to FLASH radiotherapy Secondary Objective Outcome Measures: 3. **Pain relief:** • Patient reported pain score overall and specifically for treated sites • Use of pain medication
Study Population	The study population will consist of up to 10 patients with painful bone metastasis(-es) in the extremities who are treated using FLASH radiotherapy to 1-3 sites. Patients at least 18 years of age will be considered regardless of race or gender.
Description of Study Intervention	Subjects will be treated for painful metastases in the extremities (limbs, excluding feet, hands, wrists) using FLASH radiotherapy. The FLASH enabled ProBeam Proton Therapy System, which delivers proton radiation at a FLASH dose rate, will be used for subject treatments.
Description of Sites Enrolling Participants	The study will be carried out at 1 investigational site with a ProBeam Proton Therapy System that is modified to deliver proton radiation at a FLASH dose rate.

Subject Study Participation Duration	Subjects will be on study prior to their radiation treatment simulation (approximately 1-2 weeks), during their radiation treatment simulation, plan selection, and delivery (≤ 7 business days), and during post-treatment follow-up (until subject death or lost to follow-up). In general, subjects with metastatic disease have a guarded prognosis. Their survival varies with their diagnosis and rate of disease progression. Thus, it is not possible to specify the duration of a subject's participation in the study. Subject participation may last from a few months to several years.
Study Duration	Enrollment for the study is expected to take 12 months. The study may run from 1.5 years to several years (which covers enrollment, treatment, follow-up, and completion of data analyses).

2.2.2 Schedule of Activities

		Treatment Simulation to Treatment Delivery (≤ 7 business days)				Post Treatment Follow-up						
Event	Enrollment, Baseline (~1-2 weeks)	Preparation for treatment	Prior to treatment delivery (Day 1)	Treatment delivery (Day 1)	After treatment delivery (Day 1)	Day 2 – Day 11[1] (daily)	Day 2 (+ 1 calendar day)	Day 15[2] (+/- 2 business days)	Month 1[2] (+/- 5 business days)	Month 2[2] (+/- 10 business days)	Month 3[2] (+/- 10 business days)	Long Term[3] (every 2 months, +/- 10 business days)
Patient screening (inclusion/exclusion criteria)	X											
Informed consent	X											
Demographics	X											
Disease information	X											
CT-based simulation		X										
Treatment plan selection		X										
Treatment plan QA		X										
FLASH treatment delivery				X								
Questionnaire for pain flare at treated sites[4]			X			X						
Questionnaire for overall pain assessment[4]			X					X	X	X	X	X
Questionnaire for pain assessment at treated sites[4]			X					X	X	X	X	X
Subject evaluation: review of pain medications (including steroid medications), performance status	X		X					X	X	X	X	X
Subject evaluation: physical evaluation[5]	X		X					X	X	X	X	X
Adverse Event evaluation					X		X[6]	X	X	X	X	X

[1]Day 2- Day 11 bone pain flare assessment questionnaire is completed remotely.
[2]It is desirable to have follow-up visits in-person. However, it is acceptable to carry out remote follow-up visits as an alternative in the event of the subject's inability or reluctance to travel given the current COVID-19 pandemic. In these circumstances, photographs of the treatment site may be taken at home by caregivers, and physical evaluation will be carried out to the extent that is feasible via telehealth.
[3] Long Term follow-up will continue until subject death or lost to follow-up. Following the Month 3 visit, subsequent long-term follow-up visits will take place every 2 months. Questionnaires will be completed as subject's clinical status permits. Subject evaluation (review of pain medications (including steroid medications), performance status, physical evaluation) and adverse event evaluation may be carried out using a combination of remote visits and/or records review as an alternative to in-person visits to accommodate the subject's inability or reluctance to travel.
[4]See section 2.8.6 for the description of the questionnaires.
[5]Physical evaluation includes photographs of skin at entry and exit sites of beam. These should include an image that encompasses the entire anatomic region treated (upper leg, lower leg, upper arm, lower arm), with close-up photographs of the skin in each treated area(s), if the treated area(s) is readily identifiable.
[6]Day 2 adverse event evaluation will be carried out using a remote visit.

2.3 Introduction

Rationale for evaluating FLASH radiotherapy:
Radiotherapy is one of the primary treatment modalities for the treatment of patients with cancer. Most radiotherapy is delivered using linear accelerators or cyclotrons/synchrotrons to create ionizing radiation in the form of x-rays, electrons, or protons. The radiation is delivered to cancer-containing tissue with the intent of eradicating cancer while minimizing harm to surrounding normal tissue. Creation of a favorable "therapeutic ratio" for radiotherapy damage to tumor with sparing of adjacent normal tissue is primarily accomplished through careful targeting of the tumor, conforming the delivered radiation to the target volume, and delivery of modest "sub-lethal" amounts of radiation repeatedly over time (termed "dose fractionation"). One potential strategy for increasing the therapeutic ratio that has been largely unexplored is the delivery of radiation at ultra-high dose rates.

Due to technical limitations of current radiation-generating devices, most radiotherapy is delivered at dose rates of approximately 0.03 Gy/s. Decades of experimental and clinical experience have been obtained demonstrating the safety and efficacy of radiotherapy given at these dose rates, and this is the standard of care for treating patients with cancer. More recently, radiation-generating devices have been devised that are capable of delivering much higher radiation dose rates – 40 Gy/s or greater. Radiation produced at these high dose rates has been termed "FLASH" radiotherapy since the entire fraction of radiotherapy can be delivered in less than a second.

The effects of FLASH radiotherapy have been studied in vitro and in animals with encouraging results. Compared to radiotherapy given at conventional dose rates, FLASH radiotherapy has been shown in multiple models to cause less injury to normal cells and tissue, while having equal or greater tumor cell killing. Favaudon et al. irradiated mouse lungs in vivo with both FLASH radiotherapy and conventional dose rate radiotherapy (CRT) [1]. Using a single dose of 17 Gy, 100% of mice given CRT developed pneumonitis and fibrosis whereas none of the mice given FLASH radiotherapy developed these toxicities. FLASH radiotherapy doses were escalated to 30 Gy single dose before the mice began developing pneumonitis and fibrosis. The same investigators treated orthotopic lung tumors in mice with single dose FLASH radiotherapy and CRT. 15 Gy CRT controlled tumors in only 20% of mice, most of which developed significant pneumonitis. 27 Gy FLASH radiotherapy controlled tumors in 70% of mice, none of which developed pneumonitis.

Montay-Gruel et al. treated mouse brains in vivo with 10 Gy of radiation using both FLASH radiotherapy and CRT techniques. Neurocognitive impairment developed subsequently in the CRT group whereas mice treated with FLASH radiotherapy remained functionally intact [2]. The normal tissue sparing effects of FLASH have also been observed in several other tissues and animal models including mouse intestine [3], mouse skin [4], and cat and pig skin [5]. The mechanism for FLASH is not fully understood, but there are data that suggest FLASH produces lower levels of toxic oxygen reactive species in normal tissues as compared to CRT [6].

To date, there has been one published case report of the use of FLASH radiotherapy in a human. A single patient with cutaneous T cell lymphoma and extensive prior radiotherapy to the skin was treated with electron FLASH radiotherapy for a recurrent cutaneous lymphoma lesion. A

single dose of FLASH radiotherapy using 15 Gy electron radiotherapy was delivered. This resulted in a complete response of the lesion with minimal toxicity to the surrounding skin [7].

Given the preclinical data suggesting significant reduction in normal tissue toxicity using FLASH radiotherapy compared to CRT and equivalent efficacy of treatment, we propose to assess the workflow feasibility of FLASH radiotherapy in a clinical setting, toxicities, and pain relief at the treated site(s) following treatment of painful bone metastasis(-es) in extremities.

Rationale for using protons for FLASH radiotherapy:
Currently, there is no commercially available medical linear accelerator capable of delivering x-rays at FLASH dose rates. However, some cyclotrons used to produce proton radiation for treatment of cancer have high beam currents that are capable of these dose rates. Therefore, this clinical study will be carried out at investigational sites with the ProBeam Proton Therapy System, an FDA cleared device (510(k) K133191), that utilizes a cyclotron to deliver proton radiation, and that is modified to deliver the proton radiation at a FLASH dose rate.

Rationale for selecting patients with bone metastases for study:
Patients with painful bone metastases represent an ideal population for a feasibility study of FLASH radiotherapy. These patients are known to benefit from the palliative effects of radiotherapy using single dose radiation dose regimens, similar to those tested in pre-clinical studies of FLASH radiotherapy [8] [9]. If treated off-study with CRT, these patients' photon treatment regimen and follow-up is expected to be very similar to what would be performed on-study using FLASH radiotherapy with protons. Therefore, the time and social burden imposed by study participation would be minimal and risk of toxicities would also be minimized.

Amendments to this Clinical Investigation Plan (CIP) will be made by revising the CIP and producing a "track changes" version showing changes from one version to another version.

2.4 Objectives

Primary Objective:

1. Assess workflow feasibility of FLASH radiotherapy in a clinical setting
2. Assess toxicities of treatment

Secondary Objective:

3. Assess pain relief at the treated site(s)

2.5 Outcome Measures

The outcome measures corresponding to the study objectives are as follows:

Primary Objective Outcome Measures:

1. Workflow feasibility:

- Patient time on the treatment table
- Delays in study treatment related to the investigational device (excluding delays due to patient or facility factors not related to study treatment)

2. Toxicities of treatment:

- Toxicities that are possibly, probably, or definitely related to FLASH radiotherapy Toxicities will be classified per CTCAE[1] version 5.0

Secondary Objective Outcome Measures:

3. Pain relief:

- Patient reported pain score overall and specifically for treated sites
- Use of pain medication

2.6 Study Design

This study is designed as a prospective feasibility study.

Subjects will be followed until death or lost to follow-up.

The study patients will be enrolled and undergo FLASH radiotherapy at 1 investigational site.

2.7 Study Population (Inclusion/Exclusion Criteria)

Patients with up to 3 painful bone metastasis(-es) in the extremities (limbs, excluding feet, hands, wrists) will be evaluated for this study. Only limb bones will be treated with FLASH (excluding feet, hands, wrists). Other bone metastases (i.e., non-limbs or feet, hands, wrists) may be treated with conventional radiation therapy while the patient is on study. Painful lesions of the limb bones must be treatable with fixed protocol field sizes (see below) for each limb bone lesion, without overlap of radiation fields. Patients should have expected life expectancy >2 months, in the judgement of the investigator. Women of childbearing age must verbally deny being pregnant at the time of consent (pregnancy test will be performed prior to CT simulation as per standard of care at the investigational site).

All inclusion criteria must be met and none of the exclusion criteria may be present for a patient to be eligible for the study. All eligibility criteria will be assessed prior to study enrollment.

[1] Cancer Therapy Evaluation Program (CTEP) home page: http://ctep.cancer.gov

Patients on this study may be enrolled in additional investigational studies related to their cancer treatment as long as the investigator believes this study and any other study the patient might be enrolled in would not be in conflict.

Inclusion Criteria:

- Patient age at least 18 years
- Up to 3 painful bone metastasis(-es) in the extremities[2]
- Bone metastases that can be treated using pre-defined treatment field sizes (7.5 cm x 7.5 cm; 7.5 cm x 10 cm; 7.5 cm x 12 cm; 7.5 cm x 14 cm; 7.5 cm x 16 cm; 7.5 cm x 18 cm; 7.5 cm x 20 cm), without overlap of radiation fields
- Life expectancy of >2 months (in the judgement of the investigator)
- Patients who are able to comply with the protocol
- Provision of signed and dated informed consent form

Exclusion Criteria:

- Prior radiotherapy to the treatment site(s)
- Lesions of the feet, hands, wrists are not eligible treatment sites for FLASH
- More than 3 painful bone metastases of the limbs requiring palliative radiotherapy
- Tumor lysis of >50% of the circumferential bone cortex, or other factors considered to place the subject at significant risk of pathologic fracture
- Patients with bone fractures and/or metal implants in the treatment field[3]
- Patients who will receive cytotoxic chemotherapy within 1 week prior to or 1 week following their planned radiation treatment[4]
- Prior local therapy modality to the treatment site(s) within 2 weeks of study enrollment
- Patients with pacemakers or other implanted devices at risk of malfunction during radiotherapy
- Patients with any other medical condition or laboratory value that would, at the discretion of the investigator, preclude the patient from participation in this clinical investigation
- Patients at known risk of enhanced normal tissue sensitivity to radiotherapy due to inherited predisposition or documented comorbidity that might lead to hypersensitivity to ionizing radiation
- Patients enrolled in any other clinical studies the investigator believes to be in conflict with this clinical investigation.
- Patients who are pregnant or nursing

2.8 Procedure

Study activities consist of the following:

1. Screening, Informed Consent, and Baseline Evaluation
2. CT-based Simulation

[2] Patients with more than 3 painful bone metastases of the limb bones requiring treatment are more likely to have generalized pain that may confound measurement of pain relief response to treatment
[3] Proton range and dosimetry is less certain in the presence of metal.
[4] Exclusion for concurrent therapies that may affect the tissue response to radiation.

3. Treatment Plan Selection
4. QA
5. FLASH Radiotherapy Delivery
6. Pain Assessment Questionnaires
7. Adverse Event Checks
8. Follow-Up

A detailed description of these activities is provided below. Some of the study activities occur during regular visits the subject will have as part of their oncologic care.

The FLASH radiotherapy delivery shall be performed in accordance with written instructions and training provided for this study by the Sponsor. Clinical site staff with appropriate qualifications will be trained on device usage and clinical study operations.

Sponsor representatives may attend the study procedures, with investigator and patient permission, and record observations.

2.8.1 Screening, Informed Consent, and Baseline Evaluation

Screening, Informed Consent

Patients will be informed about the study primarily by radiation oncologists and their staff. The results of the screening process will be compiled by the investigational site and the investigator will determine whether the patient meets the eligibility criteria. Patients interested in participating in the study will be asked to read, understand and sign the Informed Consent document, consistent with institutional practices. Patients who meet all eligibility criteria and sign consent may proceed onto the study.

Note that during the study, subjects will be informed of new information and asked to sign a revised Informed Consent document when requested by IRB, the Principal Investigator, or the Sponsor.

Each subject will be given a unique study identification code; the link between the identification code and the subject's identity will be maintained by the Principal Investigator. The code will be entered onto each subject's case report forms and other study records.

Replacement of subjects

Only subjects who are treated on this study protocol will be counted towards the study patient limit.

Subjects who sign the informed consent form and subsequently withdraw, or are withdrawn, from the study prior to receiving the FLASH radiotherapy will not be counted towards the study patient limit and will be replaced.

Subjects who sign the informed consent form, receive the FLASH radiotherapy, and subsequently withdraw, or are withdrawn from the study, will be counted towards the study patient limit and will not be replaced.

Baseline Evaluation

Subject characteristics will be recorded, including age, gender, performance status, history of medical comorbidities or autoimmune disorders, diagnosis date, prior cancer-directed treatments. Tumor characteristics will be recorded, including histology, anatomic location of the original primary tumor and the anatomic location of treatment site(s), target lesion size, target lesion extent of bone circumferential involvement (if available), metastasis type (i.e., lytic, blastic, mixed). Subject evaluation data will be recorded: review of pain medications (including steroid medications), performance status, photographs of skin and any physical findings on examination involving the skin or other normal tissue in the planned treatment site(s).

Subjects may continue to take steroids during their participation in the clinical trial if prescribed by their physician. Steroid medication is optional and at the discretion of the prescribing physician.

2.8.2 CT-based Simulation

Simulation imaging is performed as part of standard of care in order to develop the radiation treatment plan. During the simulation procedure, the subject is placed on the CT simulator couch in a stable and reproducible position suitable for targeting the metastatic lesion(s). Immobilization devices such as a Vac-Lok bag will be used for all subjects to aid in immobilizing the target site(s) and for reproducing the subject's positioning at the time of treatment. A CT scan will be obtained through the areas of interest and used for radiotherapy planning.

Adequate radiotherapy coverage of the target lesion(s) will be assessed using this CT during the treatment plan selection process (see section 2.8.3). This assessment will be carried out for each of the planned FLASH treatment sites (up to 3 FLASH treatment sites for each subject). Subjects who cannot be treated using the available pre-defined treatment field sizes (see inclusion criteria) will be removed from the study and replaced.

Women of childbearing age must have a negative pregnancy test at the time of CT simulation. If the pregnancy test is positive, the subject will be removed from the study and replaced. It is standard of care at the investigational site to evaluate pregnancy status for women of childbearing age at the time of CT simulation.

2.8.3 Treatment Plan Selection

The simulation CT images will be electronically transferred to the Eclipse treatment planning workstation (Varian, Palo Alto, CA; Eclipse is used without modification to the present 510(k) clearance) and the target site(s) will be delineated by one of the radiation oncologist investigators. A single-field 250 MeV transmission plan will be chosen from a pre-defined library of plans having different field sizes (see section 2.7). Based on a review of bone metastases cases treated at the investigational site over a 12-month period, these field sizes will be adequate to treat sufficient patients successfully. Plans will be matched for each of the FLASH treatment sites (up to 3 FLASH treatment sites for each subject). Using image guidance, clinical lesions up to 6.5 cm in diameter will be treated. A Planning Tumor Volume (PTV) margin of $\geq$5 mm will be added to the Gross Tumor Volume/Clinical Target Volume (GTV/CTV). There will be no GTV to CTV margin. This is consistent with standard clinical practice in the palliative

treatment of bone metastases. Patients who cannot be treated using the pre-defined treatment field sizes will be removed from the study and replaced.

The pre-defined plans are designed to deliver a prescription of 8 Gy in a single fraction at ≥40 Gy/s to the PTV. Since the treatment will be delivered with transmission FLASH, there will be no Bragg Peak within the body; the relative biological effectiveness (RBE) of 1.0 will, therefore, apply since no correction is required for Bragg Peak. The volume of PTV receiving 90% of the prescribed dose shall be greater than or equal to 90%, and the dose to 10% of the PTV will not exceed 110%. The prescribed dose of 8 Gy in a single fraction is a standard fractionation for painful bone metastases whose efficacy has been validated in prior multi-institutional prospective randomized clinical trials [10, 11].

2.8.4 QA

There are two forms of QA routinely performed for treatment with standard dose rate proton radiation. The first is daily machine QA and the second is patient specific QA. Patient specific QA for subjects treated on this FLASH study protocol may be performed, for example, using film and ion chamber dosimetry. An additional QA procedure will be performed on the day of treatment prior to the subject's treatment confirming the FLASH dose and dose rate constancy of the proton delivery system.

2.8.5 FLASH Radiotherapy Delivery (Day 1)

The treatment plan will be transferred from the ARIA Oncology Information System (Varian, Palo Alto, CA; ARIA is used without modification to the present 510(k) clearance) to the FLASH enabled ProBeam Proton Therapy System console for FLASH radiotherapy delivery. Subjects will be positioned on the treatment couch as determined at the time of their simulation visit. Image guidance will be used to verify that the target is in the correct position for treatment. The treatment will be carried out for up to 3 treatment sites for each subject, depending on the total number of painful bone metastases in limb bones (excluding feet, hands, wrists) to be treated.

On the day of treatment, but before start of treatment, the following baseline data will be recorded: patient reported pain score overall and specifically at each treated site (see section 2.8.6 for questionnaires to be used); subject evaluation (use of pain medication (including steroid medications), performance status, photographs of skin and any physical findings on examination involving the skin or other normal tissue in the treatment site(s)).

2.8.6 Pain Assessment Questionnaires

There are several questionnaires used in this study as described below:

Brief Pain Inventory (BPI) short form questionnaire:
Patient reported pain score (overall) at baseline and post-treatment (Day 15, Month 1, Month 2, Month 3, long-term) will be assessed using the BPI short form questionnaire (see section 2.2.2 Schedule of Activities table).

The BPI short form questionnaire was employed in a prior cooperative-group (Radiation Therapy Oncology Group) prospective, phase III, randomized study evaluating the efficacy of 8 Gy radiation for the treatment of painful bone metastases [10]. Using the BPI short form questionnaire will allow comparison of the current study results to these historical data. This form assesses overall pain response without focus on an individual metastasis.

Treated Sites Pain questionnaire:
Additionally, patient reported pain for each treated site at baseline and post-treatment (Day 15, Month 1, Month 2, Month 3, long-term) will be assessed using a four item subset of the questions from the BPI questionnaire (see section 2.2.2 Schedule of Activities table). This form assesses pain response in each treated site.

Pain Flare questionnaire:
An additional three item questionnaire is required only at baseline and for the first 10 days after treatment to assess radiation treatment related flare in bone pain for each treated site (see section 2.2.2 Schedule of Activities table). The questionnaire uses the methodology employed by Chow et al. [12] to specifically identify flare in bone pain. The patient reported questionnaire will be used to collect the following information: for each treated site, worst pain over the last 24 hours and comparison of this worst pain to the worst pain in the treated site on the day of treatment; pain medications usage, including steroid medications.

2.8.7 Adverse Event Checks

Adverse events will be monitored from start of treatment to completion of the final study follow-up visit. Adverse event checks will take place on the day of treatment (Day 1 after treatment delivery) and at the follow-up visit time points Day 15, Month 1, Month 2, Month 3, and long-term follow-up (see section 2.2.2 Schedule of Activities table). The adverse event check on Day 2 will be carried out by remote review. All other adverse event checks during follow-up may be carried out using a combination of remote visits and/or records review as an alternative to in-person visits to accommodate the subject's inability or reluctance to travel. Adverse event checks will be recorded on the corresponding case report form. All adverse events will be collected regardless of severity or attribution. Adverse events will be classified per CTCAE version 5.0.

2.8.8 Follow-Up

During the first 10 days after completion of FLASH radiotherapy, subjects will complete a questionnaire daily to assess radiation treatment related flare in bone pain for each treated site (see section 2.8.6 for questionnaires to be used; see section 2.2.2 Schedule of Activities table).

Subjects are expected to have in-person follow-up visits at Day 15 (+/- 2 business days), Month 1 (+/- 5 business days), Month 2 (+/- 10 business days), and Month 3 (+/- 10 business days); long-term follow-up 2 months (+/- 10 business days) beyond Month 3, until subject death or lost to follow-up.

For the Day 15, Month 1, Month 2, Month 3 follow-up visits, the following data will be recorded:

- Patient reported pain score overall and specifically at each treated site (see section 2.8.6 for questionnaires to be used; see section 2.2.2 Schedule of Activities table)
- Subject evaluation: use of pain medications (including steroid medications), performance status, physical evaluation including photographs of skin and any physical findings on examination involving the skin or other normal tissue in the treatment site(s)
- Adverse event evaluation (including skin and other normal tissue toxicities)
- It is desirable to have follow-up visits in-person. However, it is acceptable to carry out remote follow-up visits as an alternative in the event of the subject's inability or reluctance to travel given the current COVID-19 pandemic. In these circumstances, photographs of the treatment site may be taken at home by caregivers, and physical evaluation will be carried out to the extent that is feasible via telehealth.

Long-term follow-up visits beyond Month 3 may be carried out using a combination of remote visits and/or records review as an alternative to in-person visits to accommodate the subject's inability or reluctance to travel. The following data will be recorded:

- Patient reported pain score overall and specifically at each treated site (see section 2.8.6 for questionnaires to be used; see section 2.2.2 Schedule of Activities table). Questionnaires will be completed as subject's clinical status permits.
- Subject evaluation (use of pain medication (including steroid medications), performance status, physical evaluation)
- Adverse event evaluation (including skin and other normal tissue toxicities)

Follow-up visits that are in-person (Day 15, Month 1, Month 2, Month 3) and any in-person visits during long-term follow-up will take place at a location(s) listed in section 9, as determined by mutual convenience of the subject and investigator.

Choice of follow-up visit time points was informed by the study designs of Chow et al. [12] and Hartsell [10].

Patients may continue to take steroids during their participation in the clinical trial if prescribed by their physician. Steroid medication is optional and at the discretion of the prescribing physician.

Subject study participation will end following subject death or lost to follow-up.

2.9 Adverse Events

Adverse event evaluation and management will be conducted by the investigator or his/her designee (must be study physician, nurse, or PA/ARNP). Radiation dermatitis within the irradiated field is the adverse event that would be most likely to occur. This adverse event would be managed as an outpatient treatment at the locations listed in section 9 by the investigator or his/her designee using an appropriate combination of topical emollients, topical steroids, topical antibiotics, and dressings as determined to be necessary by the investigator or designee. Other adverse events that might occur such as pathologic fracture of the treated bone would be referred to the appropriate specialist for management (note that pathologic fracture of a bony metastasis is a known complication of the disease process).

The CTCAE version 5.0 defines an adverse event (AE) as follows: "Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses."

AEs will be given an attribution by the investigator as follows:

- Definitely related to the FLASH radiotherapy delivery
    - AE has timely relationships to the investigational device administration and there is no known alternative etiology responsible for the AE.
- Probably related to the FLASH radiotherapy delivery
    - AE has a timely relationship to the investigational device administration. No potential alternative etiology is apparent.
- Possibly related to the FLASH radiotherapy delivery
    - AE has a timely relationship to the investigational device administration; however, a potential alternative etiology may be responsible for the AE.
- Unlikely (Probably not) related to the FLASH radiotherapy delivery
    - There is no definitive evidence that the AE has a relationship to the investigational device. It was either present before the study, a symptom(s) of primary disease, or due to use of concomitant medications.
- Definitely not related to the FLASH radiotherapy delivery
    - There is clearly no evidence that the AE has a relationship to the investigational device.

The investigator will document whether the AE is attributable to the FLASH radiotherapy delivery.

Grades will be assigned to clinical AEs by the investigator or his/her designee per the CTCAE version 5.0, which consists of a scale from 1 to 5 to describe the severity of the AE. A copy of the CTCAE version 5.0 will be provided. For reference, an overview of the grades is given below, but the CTCAE v5 needs to be consulted for specific grading criteria:

- Grade 1 – Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 – Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- Grade 4 – Life-threatening consequences; urgent intervention indicated.
- Grade 5 – Death related to AE.

There are anticipated adverse events associated with the delivery of 8 Gy radiation in a single fraction at standard dose rate for the treatment of bone metastases. The frequency and severity of these toxicities were evaluated at standard dose rates in a prior benchmark multi-institutional prospective randomized clinical trial [10]. In this trial, a cohort of 455 patients (433 and 354 patients analyzed for acute and late toxicities, respectively) were treated with 8 Gy for palliation of painful bone metastases. Grade 2-3 acute toxicity (within 90 days after starting radiation therapy) occurred in 10% of the patients, and "late toxicity was rare (4%)". The most common toxicity was gastrointestinal, which accounted for approximately half of all acute adverse events. Gastrointestinal toxicity should not be relevant to the present feasibility study as treatment is limited to the extremities. No patients in the cited study receiving 8 Gy had Grade 4 acute or late toxicities.

It is expected that the majority of toxicities in the present clinical study will be related to the skin. In the prior cited study, there were no acute or late grade 3 or grade 4 skin toxicities in patients treated with 8 Gy at standard dose rates. Of the 433 patients, acute grade 1/ grade 2 / grade 3 / grade 4 skin toxicities occurred in 15 / 1 / 0 / 0 patients, respectively. Acute grade 1 / grade 2 / grade 3 / grade 4 hematologic toxicities occurred in 10 / 7 / 2 / 0 patients, respectively. "Other" (not specified) acute grade 1 / grade 2 / grade 3 / grade 4 toxicities occurred in 11 / 6 / 6 / 0 patients, respectively. These toxicities were scored using the (RTOG) Acute and Late Morbidity Criteria. This grading system has since been supplanted by the CTCAE system. For the great majority of toxicities (skin) expected in the present clinical study, the RTOG skin and CTCAE radiation dermatitis scoring systems are very similar. In addition, the hematologic scoring criteria for both RTOG and CTCAE are very similar or can be readily numerically converted for comparison purposes.

<u>Serious Adverse Events</u>

Per ISO 14155:2011, the following definitions apply:

- A Serious Adverse Event (SAE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device* that:
    - Led to a death,
    - Led to serious deterioration in the health of the subject, that either resulted in
        - a life-threatening illness or injury, or
        - a permanent impairment of a body structure or a body function, or
        - in-patient or prolonged hospitalization**, or
        - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Led to fetal distress, fetal death or a congenital abnormality or birth defect.

*NOTES:

- NOTE 1 This definition includes events related to the investigational medical device or the comparator.
- NOTE 2 This definition includes events related to the procedures involved.
- NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

**NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Hospitalization means admitted to hospital for at least 24 hours. An emergency room, urgent care, or infusion center visit is not a hospitalization.

Per the US Code of Federal Regulations, Title 21, Part 812, the following definition applies:

- Unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Event Reporting

The Investigator will notify the Sponsor of all serious adverse events (SAEs), including UADEs, by phone or email as soon as possible but no later than within 24 hours of learning of an event.

Sponsor Contact Information for Adverse Event Reporting:

Jennifer Woo
Jennifer.Woo@Varian.com

Lisa Levine, PhD
Lisa.Levine@Varian.com
[redacted] (voicemail) or [redacted] (mobile)

It is the responsibility of each Investigator to report all reportable adverse events and other reportable events to the Institutional Review Board (IRB) according to the requirements of the IRB.

Per the US Code of Federal Regulations, UADEs will be reported and evaluated as required in 21 CFR Part 812.

2.10 Device-Related Issues

Any problems with the FLASH radiotherapy delivery (including any device failures or malfunctions) will be documented and reported to the Sponsor.

Per ISO 14155:2011, the following definition applies:

- Device Deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

  NOTE Device deficiencies include malfunctions, use errors, and inadequate labeling.

2.11 Protocol Deviations and Other Study Problems

The investigator is not allowed to deviate from the CIP, except in emergency situations in order to protect the rights, safety, and well-being of the subjects. Protocol deviations and other problems with study execution will be documented and reported to the Sponsor and the IRB promptly.

2.12 Subject End of Study

The Subject End of Study case report form will be completed in the following situations:

- The subject completed the study per protocol
- The investigator terminated the subject's participation
- The subject withdrew from the study
- The subject was lost to follow-up (after a minimum of two phone calls on separate days and within a week of a certified letter being delivered)
- The subject died on study
- The Sponsor terminated the study

If the subject leaves the study for any reason before the next scheduled follow-up visit is completed, the investigator will document the reason(s). In addition, the investigator will attempt to collect the following: patient reported pain score overall and specifically for treated site(s), use of pain medications (including steroid medications), and adverse events (including skin and other normal tissue toxicities).

An investigator may withdraw the subject's participation in the study for one or more of the following reasons:

- Significant non-compliance with the study procedures

- If an adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

2.13 Planned Analyses, Sample Size, and Stopping Rules

The Sponsor will conduct the following analyses corresponding to the study objectives and prepare a clinical study report. Where appropriate, descriptive statistics will be used.

Primary Objective:

1. **Workflow feasibility:**
   For each subject, workflow feasibility will be judged as successful or not based on the following criteria:

   Treatment for an individual subject will be deemed NOT feasible if:
   - Total treatment time on table is greater than one hour OR
   - A delay in study treatment of more than 7 business days from simulation to treatment occurs related to the investigational device (excluding delays due to patient or facility factors not related to the study treatment)

2. **Toxicities of treatment:**
   All toxicities will be tabulated and summarized. Toxicities that are possibly, probably, or definitely related to FLASH radiotherapy will be used for the assessment of toxicity of the FLASH treatment.

   Note: A dose-limiting toxicity (DLT) is defined as a Grade $\geq$3 toxicity attributed as possibly, probably, or definitely related to FLASH radiotherapy. The number of DLTs will be monitored through the duration of the study and will be used as a criterion in the Stopping Rules (see section 2.13 for a Stopping Rule related to DLT.)

Secondary Objective:

3. **Pain relief:**
   As discussed above in section 2.8.6 patient reported pain score (overall) at baseline and post-treatment (Day 15, Month 1, Month 2, Month 3, long-term) will be assessed using the Brief Pain Inventory (BPI) short form questionnaire. Patient reported pain score for each treated site will be assessed using the Treated Sites Pain questionnaire.

   The BPI short form questionnaire was selected to permit the results of this study to be compared with prior published results using this instrument [10].

   Per the methodology of Hartsell, et al. [10]: The worst pain score in the BPI short form will be used to assess treatment response; a complete response will be defined as having no pain at 3 months after radiation therapy; a partial response will be defined as a pain score that is at least two points lower than the initial response; a stable response

will be defined as a one-point change in pain score in either direction; a progressive response will be defined as a pain score that is at least two points higher than the initial score. The same analysis will be applied to the individual sites treated by FLASH, as assessed by the questionnaire with the four-item subset of the BPI questionnaire.

Per the methodology of Chow et al., flare in bone pain due to radiation will be assessed using the Pain Flare questionnaire administered on Day 1 - Day 11. Pain flare is defined as either of the following: a minimum of a two-point increase in the worst pain score for the treated site without a reduction in analgesic intake; or a 25% or greater increase in analgesic intake based on daily oral morphine equivalence without a reduction in the worst pain score. If the worst pain score before treatment was nine or ten, the criteria for pain flare were met if the follow-up worst pain score was ten and reported as worse than the worst pain before treatment with no decrease in analgesic intake. To distinguish pain flare from progression of pain, the worst pain score and analgesic intake had to return to baseline levels during the 11-day (Day 1 - Day 11) time period. Consistent with the Chow study, we will document use of steroid medication.

Data on use of pain medication will be collected and changes in pain medication use will be evaluated between baseline, during each of the first 10 days after treatment, and follow-up visits (Day 15, Month 1, Month 2, Month 3). The percentage of patients requiring narcotic, non-narcotic analgesics, and no pain medications will be assessed and compared to literature values from prior clinical trials.

Sample Size:
For this feasibility study, a sample size of up to 10 patients will apply.

Stopping Rules:
Triggering of a stopping rule will result in a cessation of enrollment and in a review of the study data by the Cincinnati Cancer and Blood Disease Institute Data Safety Monitoring Board and Study Committee (PI and co-investigators).

The study will be stopped if any of the following occurs:

- 3 subjects experience a dose limiting toxicity (DLT) (see section 2.13 for definition of DLT)
- 3 subjects have time on the treatment table >1 hour
- 3 subjects have a delay in study treatment of more than 7 business days from simulation to treatment related to the investigational device (excluding delays due to patient or facility factors not related to the study treatment.)
- A major device malfunction in dose delivery (as indicated by the dose monitoring system). This includes potential recordable or reportable medical events under the Ohio Department of Health classification.

2.14 Data Collection and Monitoring

Data collection may include the following:

- Case report forms (electronic and/or paper)
- Images from CT scans, planar x-ray, and other radiographic-based imaging
- Dosimetry data from the selected treatment plan (printouts and/or electronic files)
- Treatment delivery log files from the FLASH enabled ProBeam Proton Therapy System
- Photographs (skin)
- Written or emailed feedback from the investigators
- Written or emailed observations from Sponsor representatives
- Responses to data queries
- Copies of pertinent records in connection with the study, including patient charts, laboratory data, etc., will be made available to the Sponsor on request with due precaution towards protecting the privacy of the patient.

Data on the case report forms will be supported by source documentation. Physician comments and feedback may be recorded directly in the case report forms.

All required data will be recorded on case report forms and/or collected in another format. All data will be reviewed by a clinical monitor from the Sponsor or a representative of the Sponsor to ensure acceptable accuracy and completeness. If necessary, the study site will be contacted for corrections and/or clarifications.

All efforts will be made to remove patient-identifying information and de-identify the data. Only the minimum necessary information regarding the patient's health records and treatment while participating in this study will be collected. All reasonable efforts will be made to protect the privacy of the patient.

Standardized electronic case report forms and case report form completion guidelines will be created for collection of study data within an electronic data capture system provided by the Sponsor. Automated edit checks, queries and audit trail are built into the system to ensure accurate data collection. Data will be transmitted via secure Internet connection to the electronic data capture system using industry-standard encryption modalities. Data access will be password protected. The Principal Investigator will be responsible for ensuring electronic case report forms are completed accurately and in a timely manner.

The Principal Investigator will maintain adequate and accurate records (per 21 CFR part 812.140(a) Investigator Records) to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents and study related documents.

2.15 Records Retention

The clinical study records may be discarded only upon notification from the Sponsor. To avoid error, the Investigator will contact the Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. Records are to be retained and securely stored after completion or discontinuation of the study for 5 years after completion of the last patient on study.

3 Risk Analysis

The clinical risk analysis is presented in this section. The justification for the investigation and a description of the study population are provided.

3.1 Risks and Mitigations

A risk with any modality of radiation therapy, including FLASH radiotherapy, is harm to normal tissues that are included within the treatment volume. In the case of FLASH radiotherapy, the side effects are expected to have the same spectrum of symptoms or physical findings that can result from conventional photon radiotherapy at conventional dose rates. Preclinical data suggests that FLASH radiotherapy may result in less toxicity to normal tissues.

Potential risks/toxicities in this clinical study:

- Skin
  - Red skin
  - Weeping of skin
  - Ulceration of skin
  - Necrosis
  - Fibrosis
  - Hyper- or hypopigmentation
  - Hair loss in the treated area
- Swelling in the extremities (lymphedema)
- Potential damage to other normal tissues in the radiation field, including to muscle, nerve, and/or bone
- Insufficient pain relief
- Fracture at the metastasis site
- Decreased blood cell count
- Radiation related secondary malignancy

Patients who are pregnant or nursing are excluded from the study because radiation treatment can pose risk to an unborn or nursing child.

The machine and patient specific QA processes outlined in section 2.8.4 are in place to verify that the correct dose is delivered as prescribed.

In the event of an interrupted FLASH treatment (as sometimes can occur with standard dose rate radiation treatment delivery), treatment may be resumed and the system will correctly execute the remainder of the plan such that the full absorbed dose of 8 Gy will be delivered to the target volume. If a spot is partially delivered, the system automatically recalculates the maximum allowed beam current to complete the remaining monitor units for that spot. This may reduce the dose rate for the remainder of the field. The potential normal tissue sparing benefit of the FLASH dose rate may be less. However, treatment can be completed likely

without any reduced effect in treating the tumor. Based on reliability testing, treatment interruption is unlikely to occur.

3.2 Justification for the Investigation

This study is designed to assess the workflow feasibility of delivering FLASH radiotherapy in a clinical setting, toxicities of treatment, and pain relief at the treated sites. It is expected that the subjects with painful bone metastasis(-es) treated on this study protocol will receive the same benefits in terms of pain control as if treated with conventional dose rate photon radiotherapy. Normal tissue toxicity is expected to be no more than and potentially less than from treatment with conventional dose rate photon radiotherapy. The clinical implementation data acquired in this investigation will contribute to optimizing FLASH enabled ProBeam Proton Therapy System workflows and making this technology routinely available to radiation oncologists and their patients.

3.3 Study Population

The study population will consist of up to 10 patients with painful bone metastasis(-es) in the extremities who will be treated using FLASH radiotherapy to 1-3 sites. Patients at least 18 years of age will be considered regardless of race or gender.

4 Description of Device

The ProBeam Proton Therapy System is an FDA Class II and an EU MDR Class IIb medical device that incorporates a superconducting cyclotron that produces 250 MeV protons. A degrader followed by an energy selector is used to vary the proton beam energy. The adjusted energy, current, and size of the proton beam is sequentially channeled to a treatment room using a beamline. A treatment room is equipped with a robot-mounted treatment table and, in many installations, a gantry to allow the proton beam to be applied to a patient from all directions.

The FLASH enabled version of the ProBeam Proton Therapy System is being developed under the regulations pertaining to 21CFR 820. This FLASH enabled device is a modified and tested ProBeam Proton Therapy System with the ability to deliver pre-defined high dose rate plans of fixed field sizes and total dose, using a specific treatment workflow. These pre-defined plans will be delivered with a minimum dose rate to the target volume of 40 Gy/s and a maximum fluctuation of 10% around the mean.

No changes are anticipated to the device during the clinical investigation.

5 Monitoring Procedures

The study will be monitored according to US FDA regulations and Good Clinical Practices.

The study monitor is:

Jennifer Woo
Jennifer.Woo@Varian.com

The Sponsor's medical monitor is:

Kenneth J. Russell, MD (Radiation Oncologist)
Ken.Russell@Varian.com
[redacted] (voicemail) or [redacted] (mobile)

The Investigator and the investigating sites will permit authorized clinical research personnel, auditors and clinical monitors from the Sponsor and/or designee(s) employed by the Sponsor, the IRB, the FDA and other applicable regulatory agencies to review subject medical records, source documents, completed case report forms, IRB decisions, and Investigator and clinical site records at regular intervals throughout the study. Subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations and/or hospital policies prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor.

Monitoring procedures are provided separately.

6 Additional Records and Reports

No other records or reports are anticipated.

7 Labeling

The "For Investigational Use Only" label for the FLASH enabled ProBeam Proton Therapy System is:

FLASH enabled ProBeam Proton Therapy System
CAUTION-Investigational Device. Limited by Federal (or United States) Law to Investigational Use.

The Instructions for Use document is provided separately.

8 Informed Consent Materials

A sample informed consent form is provided separately.

9 Investigational Site, Institutional Review Board, Principal Investigator, and Chair

Investigational Site:
This clinical study will be carried out at Cincinnati Children's Hospital Medical Center. The study activities may take place at the following locations:

Cincinnati Children's Proton Therapy Center
7777 Yankee Road Liberty Township
Cincinnati, OH 45044

Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229

Barrett Cancer Center
234 Goodman Street,
Cincinnati, OH 45219

The following study activities related to the FLASH radiotherapy will take place at the Proton Therapy Center location: CT-based Simulation, Treatment Plan Selection, QA, FLASH Radiotherapy Delivery.

All other study activities may take place at any of the three locations.

IRB:
Cincinnati Children's Hospital Institutional Review Board
3333 Burnet Avenue, MLC#7040
Cincinnati, OH 45229

IRB Chairperson: Robert Frenck, MD

Principal Investigator and Chair:
John C. Breneman, MD
Professor of Radiation Oncology and Neurosurgery in the College of Medicine
University of Cincinnati Medical Center
234 Goodman Street Cincinnati, OH 45219

Vice Chair:
John P. Perentesis, MD
Director, Cancer and Blood Disease Institute

Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229

This clinical study will be reviewed and approved by the FDA and IRB prior to participation by any patients. Any requirements imposed by the FDA and IRB will be followed. The investigator(s) will comply with all relevant human subject protection requirements including informed consent. The study will be conducted in compliance with this clinical investigational plan, US FDA Good Clinical Practices (GCPs), applicable state and local regulations, and IRB requirements.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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.

Curriculum vitae for each investigator will be maintained by the Sponsor.

10 Institutions

No other institution will participate or be used for any part of the investigation.

11 References

[1] V. Favaudon, L. Caplier, V. Monceau and et al., "Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice," *Sci Transl Med,* vol. 6, no. 245, p. 245ra293, 2014.

[2] P. Montay-Gruel, K. Petersson, M. Jaccard and et al., "Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s," *Radiother Oncol,* vol. 124, no. 3, pp. 365-369, 20017.

[3] J. B. Loo, E. Schuler, F. Lartey and M. Rafat, "Delivery of ultra-rapid flash radiation therapy and demonstration of normal tissue sparing after abdominal irradiation of mice," *Int J Radiat Oncol Biol Phys,* vol. 98, no. 2 suppl, p. E16, 2017.

[4] S. Field and D. Bewley, "Effects of dose-rate on the radiation response of rat skin," *Int J Radiat Biol Relat Stud Phys Chem Med,* vol. 26, no. 3, pp. 259-267, 1974.

[5] M. Vozenin, P. De Fornel, K. Petersson and e. al., "The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients," *Clin Cancer Res,* vol. 25, no. 1, pp. 35-42, 2019.

[6] P. Montay-Gruel, M. Acharya, K. Petersson and et al., "Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species," *Proc Natl Acad Sci U S A.,* vol. 116, no. 22, pp. 10943-10951, 2019.

[7] J. Bourhis, W. Sozzi, P. Jorge and e. al., "Treatment of a first patient with FLASH-radiotherapy," *Radiother Oncol,* vol. 139, no. 18, pp. 18-22, 2019.

[8] P. Foro Arnalot, A. Fontanals, J. Galceran and et al., "Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction," *Radiother Oncol,* vol. 89, no. 2, pp. 150-155, 2008.

[9] M. Shuja, A. Elghazaly, A. Iqbal and et al., "Efficacy of 8 Gy Single Fraction Palliative Radiation Therapy in Painful Bone Metastases: A Single Institution Experience," *Cureus,* vol. 10, no. 1, p. e2036, 2018.

[10] W. Hartsell, C. Scott, D. Bruner and et al., "Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases," *J Natl Cancer Inst,* vol. 97, no. 11, pp. 798-804, 1 June 2005.

[11] R. McDonald, K. Ding, M. Brundage and e. al., "Effect of Radiotherapy on Painful Bone Metastases: A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23," *JAMA Oncol,* vol. 3, no. 7, pp. 953-959, 2017.

[12] E. Chow, R. Meyer, K. Ding and e. al., "Dexamethasone in the prophylaxis of radiation-induced pain flare after palliative radiotherapy for bone metastases:a double-blind, randomised placebo-controlled, phase 3 trial," *Lancet Oncol,* vol. 16, pp. 1463-72, 2015.