Protocol Title: Phase II non-randomized Trial of Stereotactic Ablative Radiotherapy (SABR) for Oligometastases

Protocol Number: N/A

Version Number: 10.0

Study Phase: Phase II

Short Title: SABR-5

Sponsor Name: Dr. Robert Olson, MD (Radiation Oncologist)

[BC Cancer – Centre for the North]

Version 1.0: 07 Nov 2016
Version 2.0: 05 Dec 2016
Version 3.0: 06 Feb 2017
Version 4.0: 31 Mar 2017
Version 5.0: 17 Apr 2018
Version 6.0: 09 Oct 2018
Version 7.0: 20 Jun 2019
Version 8.0: 20 Apr 2020
Version 9.0: 17 Aug 2020
Version 10.0: 22 Aug 2022

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I. Signature of Principal Investigator

I agree to the terms of this clinical trial protocol and all amendments. I will conduct the trial in compliance with all stipulations of the protocol, according to the principles of ICH Good Clinical Practice (GCP) and any applicable local regulations.

	24 Aug 2022
Dr. Robert Olson, MD, Radiation Oncologist	**Date**
(print name and sign)	

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II. LIST OF ABBREVIATIONS

Abbreviations	Description of Abbreviations
AE	Adverse event
CBCT	Cone beam computed tomography
CI	Confidence Interval
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
GCP	Good Clinical Practice
GTV	Gross tumor volume
Gy	Gray (unit)
ICF	Informed consent form
ICH	International Council for Harmonization
IMRT	Intensity-Modulated Radiation Therapy
KV	Kilo voltage
LFT	Liver function test
LN	Lymph node
MRI	Magnetic Resonance Imaging
MV	Mega voltage
OS	Overall Survival
PBT	Proximal bronchial tree

PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression free survival
PFT	Pulmonary Function Test
PI	Principal Investigator
PSMA	Prostate Specific Membrane Antigen
POSI	Positive Outcomes and Support Initiative
PR	Partial response
PTV	Planning target volume
QoL	Quality of Life
REB	Research Ethics Board
RECIST	Response evaluation criteria in solid tumors
RFA	Radiofrequency ablation
RO	Radiation Oncologist
SABR	Stereotactic Ablative Radiotherapy
SAE	Serious adverse event
SOP	Standard Operating Procedure
SPI	Study Principal Investigator
Tx	Treatment
VMAT	Volumetric-modulated arc therapy
4D	4-dimensional

1. Protocol Summary

1.1. Synopsis

Date and Version # of Protocol:	17 Aug 2020, Version 9.0
Sponsor: BC Cancer	**Protocol Number: n/a**
Name of Study Method: Clinical Trial	**Phase of Development:** Phase II

Title of Study:
Phase II Non-randomized Trial of Stereotactic Ablative Radiotherapy (SABR) for Oligometastases

Study Design Overview/Rationale:
This is a Phase II trial assessing quality of life and side effects in patients/subjects* with up to 5 newly diagnosed or progressing metastatic cancer lesions treated with a comprehensive oligometastatic SABR treatment program. Secondarily we will document the disease free and overall survival.
*Note that patients and subjects are used interchangeably in this document.

Trial Design:
This is a non-randomized phase II trial where all subjects will receive experimental SABR to 5 newly diagnosed or progressing sites of metastatic disease. We will accrue 400 subjects to assess toxicity associated with this experimental treatment.

Radiation Treatment Plan

Eligibility
Appendix A: Eligibility Checklist
Staging

Oligometastases Entry/Registration Form (Staging)
• Brain CT or MRI within 14 weeks of subject registration for sites with propensity for brain metastases
• Body Imaging within 14 weeks of subject registration
  ○ CT scan of chest/abdomen/pelvis, with or without bone scan (at discretion of study doctor), if no PET/CT is performed
  ○ PET/CT for PET+ tumors or PSMA-PET
  ○ MRI spine for patients with vertebral or paraspinal metastases
• Bloodwork as per standard of care
• Pregnancy test for women of child bearing potential

Assessment
Oligometastases Entry/Registration form (Assessment) • ECOG Status • Documentation of site(s) of disease • Able to treat all active sites with ablative intent • Number of progressing metastases (max 5) • Prior Chemotherapy history documented

Appendix B: PATIENT-REPORTED QUALITY OF LIFE – POSI
Treatment Volumes
GTV= gross disease on CT, MRI, or PET/CT CTV not generally used. Exceptions: 1) liver = GTV + 5mm 2) spine per provincial SABR spine protocol PTV= GTV (or CTV where applicable) + 2-5 mm; 2 mm for spinal and brain tumours, 5 mm for all other sites
Pre-Tx Simulation Imaging
• 4D CT should be acquired for moving tumors. • If 4DCT is not possible, 3DCT is acceptable. • Planning CT slice thickness <= 2.5 mm. (exception: spine SABR – slice thickness = 1.25 mm) • Intravenous contrast could be used at the discretion of the treating radiation oncologist. • Fiducial markers could be used at the discretion of the treating radiation oncologist.
Prescription Isodose
PTV: V100% = 95% PTV: V 90% > 99%

Dose and Fractionation: Location	**Dose (Gy)**	**Fractions**	**Frequency**
Peripheral Lung	48 or 54	4 or 3	Daily or every other day
Central Lung -within 2 cm of PBT	60	8	Daily
Bone (including spine primary or retreatment)	35 or 24	5 or 2	Daily
Liver	54	3	Every other day
Adrenal	40 or 60	5 or 8	Daily
LN/Soft Tissue	40	5	Daily
Brain	BC Cancer Stereotactic radiosurgery protocol		

Verification Imaging	**Frequency**	**Purpose**
Pre-Tx CBCT	Daily	Move to match
Post-Tx CBCT	Day 1 or at RO discretion	Assess intra-fraction movement

Immobilization

- Immobilization devices need to be approved by the practicing Radiation Oncologist(s) and SABR physics and dosimetry staff within the particular institution.
- It is left at the discretion of the treating RO/Medical Physicist to determine which immobilization device is to be used based on their centre/department specific policy.

Disease Assessment:

- Patient Reported Quality of Life
- Toxicity (as per Common Terminology Criteria for Adverse Events (CTCAE) v.4)
- Overall Survival
- Disease-free Survival

Study Population

Patients with up to 5 newly diagnosed or progressing metastatic cancer lesions

Study Objective(s):

Primary Objective: To assess quality of life and side effects in patients with up to 5 newly diagnosed or progressing metastatic cancer lesions treated with a comprehensive oligometastatic SABR treatment program

Secondary Objective: To document disease free and overall survival

Number of Subjects/Sample Size Calculations
400 subjects will be accrued.

Planned Study Period:
Anticipated length of study is 8 years. Anticipated recruitment end date: 30 June 2020. Anticipated end date for all follow-up: 30 September 2025.

Inclusion Criteria:

Subjects must meet all of the following criteria to be eligible for participation in this study:

- Age 18 or older
- Able to provide informed consent
- Histologically confirmed malignancy with metastatic disease detected on imaging.
  - Biopsy of metastasis is preferred, but not required.
- Primary tumour treated radically or controlled by prior palliative radiotherapy or systemic therapy
- Maximum 5 metastases eligible for SABR (either 5 in total or 5 not controlled by prior treatment)
- Standard of care tests prior to SABR CT simulation within 14 weeks of patient's registration date:
  - Brain CT or MRI imaging (for tumour sites with propensity for brain metastasis)
  - Body imaging:
    - CT chest/abdomen/pelvis, with or without bone scan (at discretion of study doctor), required if no PET-CT is performed
    - PET-CT or PSMA-PET is only required for specific evidence-based indications, and in such cases the CT neck/chest/abdomen/pelvis and bone scan are not required:
    - MRI spine for patients with vertebral or paraspinal metastases
  - For other indications, at the discretion of the treating oncologists, e.g. PET-CT scans may be done but are not required.
  - Blood tests as per standard of care
  - Negative pregnancy test (urinalysis) for women of child-bearing potential within 4 weeks of RT start date
- ECOG performance status 0-2
- All sites of progressive disease can be safely treated based on criteria below:
  - For non-brainstem metastases, maximum size of 3cm if using single fraction radiosurgery.
    - If size is from 3.1 to 4cm, 25-35Gy/5 can be considered
  - All brain metastases cases need approval from Stereotactic Radiosurgery (SRS) rounds
    - Maximum size of 6 cm for lesions outside the brain, except:
  - Bone metastases over 6 cm may be included, if in the opinion of the local PI it can be treated safely (e.g. rib, scapula, pelvis)
- Life expectancy > 6 months

- In many scenarios, this is best estimated by a multidisciplinary opinion from disease site experts, often obtained by presentation at multidisciplinary tumours rounds.

- Not a candidate for surgical resection at all sites: surgery to all sites not recommended by multidisciplinary team, or unfit or declining surgery.
- No chemotherapy agents (cytotoxic, or molecularly targeted agents) will be used within the period of time commencing 2 weeks prior to radiation, lasting until 1 week after the last fraction. Certain chemotherapy agents may require a longer break prior to or after SABR if protocols dictate. Hormonal therapy during SABR is allowed.
- Patients with metastases that have been previously treated may be eligible for this SABR protocol:
  - If the previous treatment was systemic therapy, the patient may be eligible, if the metastases have demonstrated a complete radiologic response
  - If the previous treatment was by a local non-radiation means (e.g. prior resection, RFA or microwave ablation), then SABR may be considered for residual/recurrent disease
  - If the previous treatment was SABR, the **patient is not eligible** unless the new site(s) was/were not previously treated
- If the previous treatment was conventional RT, SABR could be considered if it can be delivered safely. In such a circumstance it **must** be presented in a multidisciplinary setting for approval.
- Review and consensus by 3 disease site experts, or tumour group conference, for eligibility/prognosis
- Patient is able and willing to complete quality of life questionnaires in English, and other assessments that are a part of this study, via paper or online using REDCap (if email address is provided by participant on the informed consent)

Note: The potential treating SABR radiation oncologist reserves the right to require a multidisciplinary note documenting life expectancy, other treatment options and suitability for SABR.

Waivers to the inclusion criteria will NOT be allowed.

<u>Exclusion Criteria:</u>

- Serious medical co-morbidities precluding radiotherapy
- Bone metastasis in a femoral bone if risk of pending fracture is high
- Patients with 1-3 brain metastasis and no disease elsewhere (these patients should not be accrued but treated with stereotactic radiotherapy as per results of published randomized trials)
- Complete response to first-line chemotherapy (i.e. no measurable target for SABR)
- Persistent malignant pleural effusion
- Inability to treat all sites of progressing disease with ablative intent
- Clinical or radiological evidence of spinal cord compression
- Dominant brain metastasis requiring surgical decompression
- A candidate for an open randomized clinical trial comparing SABR to a standard treatment
- Pregnant or lactating women

Waivers to the exclusion criteria will NOT be allowed.

Concomitant Medication Restrictions or Requirements:

Requirements:

Previous systemic, radiation, and hormone therapy is permitted. Hormone therapy is allowed during SABR treatment.

All cancer-specific concomitant medications that the subject is using should be recorded.

Restrictions:
No chemotherapy agents (cytotoxic, or molecularly targeted agents) will be used within the period of time commencing 2 weeks prior to radiation, lasting until 1 week after the last fraction. Certain chemotherapy agents may require a longer break prior to or after SABR if protocols dictate.

Schedule of Study Assessments and Procedures:
For Schedule of Assessments refer to Section 4.8.

Adverse Events Determination and Reporting:

Grade 1 toxicities such as mild fatigue, nausea, vomiting, skin irritation, pain, loss of appetite and some physical function are common and expected side effects of radiation therapy and therefore should not be reported as adverse events, if the event is documented in the subject's medical record[16].

Only Grade 2 or higher toxicities that are possibly, probably, or definitely related to SABR will be documented and reported as adverse events (AEs)/serious adverse events (SAEs).

Any Grade 4 or 5 adverse event that is *definitely*, *probably*, or *possibly* the result of protocol treatment must be reported to the Study Principal Investigator within 24 hours of discovery, and to the approving research ethics board (REB) as per their reporting guidelines.

Local and non-local SAEs will be reported to the applicable REB as per their reporting guidelines.

NOTE: Conditions that are NOT considered a SAE in this protocol are not included in reporting requirements, e.g., hospitalizations for routine procedures, disease progression, or death from disease progression

Formal Stopping Rules:

If any Grade 5 Serious Adverse Events (SAEs) definitely, probably, or possibly related to protocol treatment occur, all co-investigators will be made aware within 1 week of reporting to the principal investigator (PI), and a SABR-5 Toxicity Committee meeting will be held within one month of the event. During this time, any other patients on treatment to the same body site where the Grade 5 toxicity was interpreted to originate, (e.g. adrenal metastases) will have their plan reviewed by the PI to determine if that patients' treatment should be put on hold prior to SABR-5 Toxicity Committee meeting.

If 3 or more Grade 5 SAEs meet the definition of unanticipated problem (i.e. unexpected, related and involving greater risk occur during this study, as defined in Section 8.0)), the study will be temporarily put on hold in order to organize a SABR-5 Toxicity Committee meeting and initiate conversations with the BC Cancer/UBC REB. Depending on the results of these meetings, the study may be permanently closed or significant modifications may be made and re-reviewed by the REB (e.g. remove treatments of adrenal metastases from the study, or reduce the dose, if toxicity was from this body part treatment with SABR).

Statistical Evaluations:

- **Quality of Life:** Descriptive statistics - changes in patient-reported QOL before and after treatment
- **Toxicity:** Prevalence of various SAE graded events at different time intervals for a patient (ex. at 1 year, 2 years). Cumulative incidence will be used to capture multiple episodes of an SAE.
- **Survival outcomes**: Overall survival will be measured as time until death from any cause, and progression-free survival as time to either progression or death, whichever occurs first.
- **Lesion control rate** will be assessed retrospectively as RECIST criteria have not been validated in the setting of SABR, and is costly to implement in a prospective cohort.

Endpoints for Evaluation:

Primary Endpoints

- Patient Reported Outcomes (quality of life and side effects)
- Toxicity Assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4

Secondary endpoints:

- Disease-free survival
- Time from SABR treatment to disease progression at any site or death
- Overall survival
- Lesional control rate, defined as lack of further progression
- Time to starting or re-starting chemotherapy for current cancer
- Number of cycles of further systemic therapy for current cancer

2. Introduction

2.1. Trial Rationale and Background

The oligometastatic state was first defined in 1995 and refers to a stage of disease where cancer has spread beyond the site of origin, but is not yet widely metastatic.[1] In such a state of limited metastatic disease, it is hypothesized that eradication of all sites of metastatic disease could result in long-term survival, or even cure, in some patients.[2] Ablation of metastatic deposits can be achieved through several techniques, including surgery, radiofrequency ablation (RFA), or through Stereotactic ablative body radiotherapy (SABR), a new radiotherapy technology that delivers very large, hypofractionated doses of radiotherapy to small tumour targets, with high rates of local control.

Clinical evidence to support the presence of an oligometastatic state is controversial. However, there is emerging low quality evidence in both the surgical and SABR literature that this state may exist. In a study of over 5200 patients with lung metastases who underwent surgical resection, a 5-year survival of 36% was reported in patients who achieved a complete resection, much higher than would be expected for stage IV disease.[3] Similarly, in patients treated with SABR for 1-3 lung metastases from a variety of primary tumours, local control with SABR was 96% at 2-years, and 2-year survival was 39%.[4] Long-term survival has been demonstrated in patients treated for oligometastases with surgery or SABR at several other tumour sites, including liver, brain, bone, and adrenal metastases.[2,5-8] The risk of further metastases after ablative treatment is up to 60-80% in some studies.[4,5] SABR can also be used for further salvage at newly progressive sites (oligoprogression).[9]

Despite the apparent achievement of long-term survival with ablative treatment for oligometastatic disease, the level of evidence to support such treatments is weak, often based on single-arm studies without appropriate controls.[10] Patients included in such reports are highly selected, based on good performance status and slow pace of tumour progression. It has been suggested that the long-term survival achieved with treatment of oligometastases is a result of the selection of fit patients with very slow-growing tumours, rather than the result of treatment intervention. [11]

Randomized trials are therefore necessary to establish the utility of ablative treatment of oligometastatic disease,[10,12] ***and therefore the BC Cancer oligometastatic SABR group recommends that patients be offered a randomized control trial, if available, rather than being offered SABR on this current trial.*** BC Cancer has decided that given the limited evidence for SABR in this setting, it will not be offered off trial. ***The main focus of this trial is to assess the side effects and quality of life post SABR.*** This trial aims to provide a clear informed consent process, including the limited evidence for SABR off trial and potential harm from SABR (see section 2.2.1 and ICF for summary of risks and benefits) for patients opting to pursue SABR for oligometastases.

2.2. Radiation Treatment Overview

2.2.1. Stereotactic Ablative Radiotherapy (SABR)

The guiding principle for SABR is to achieve disease control and minimize any potential adverse impact on QoL. Doses and fractionations by tumour site are shown in Table 1 (Appendix D).

All patients will undergo planning CT simulation. 4-dimensional CT will be used for tumours in the lungs or upper abdomen. Axial CT images will be obtained throughout the region of interest. For all lesions, the gross tumour volume (GTV) will be defined as the visible tumour on CT and/or MRI imaging +/- PET. Consistent with international consensus guidelines, clinical target volume (CTV) expansion will be limited to vertebral and some bone lesions[7]. For mobile tumours, tumour tracking or gating can be employed at the discretion of the institution.

Alternatively, an internal target volume (ITV) can be created which encompasses all tumour motion from the 4D CT scan. For all CTVs or ITVs, a Planning Target Volume (PTV) margin of 2-5 mm will be added depending on site of disease, immobilization, and institutional set-up accuracy: 2 mm margins may be used for spinal stereotactic treatments, 2 mm for brain tumours, and 5 mm for other sites. Organs at risk visible in the planning CT scan will be contoured. Constraints and references to their source are shown in Table 2 (Appendix D).

Potential side effects from SABR will depend on the area being treated. The side effects listed below are for SABR:

- Radiation treatments to the head and neck area or brain may commonly cause headache, hair loss, mild sunburn of the skin, decreased hearing or irritation of the ears, dryness or irritation of the eyes and dry or sore mouth or throat or loss of taste during radiation treatments. Common delayed (more than 6 months after treatment) side effects from radiation treatments to the head and neck area may include persistent dry mouth (common) as well as changes in thinking or memory (rare and only if the brain is treated).
- Radiation treatments to the chest area may commonly cause dry cough, sore throat or difficulty swallowing as well as mild sunburn of the skin. Delayed (late, more than 6months post treatment) side effects from radiation treatments to the chest area may rarely cause new or persistent difficulties with swallowing; shortness of breath or cough.
- Radiation treatments to the abdomen or pelvic area commonly include diarrhea or cramping of the bowels, discomfort or frequency of urination and possibly nausea. Rarely, delayed (late, more than 6months post treatment) side effects from radiation treatments may occur including persistent cramping, diarrhea or bleeding from the bowel; frequency or discomfort with urination or bleeding from the bladder.
- Radiation treatments to bone can be associated with increased pain, redness of the skin, and a risk of a broken bone.

- Fatigue during and following radiation treatments to any of these areas is common
- Radiation treatments are associated with a small risk of serious injury to tissues or organs that are included in the area being treated. This injury may show up months to years post treatment. In very rare instances, these side effects may result in death. Some of these side effects include (depending on whether these areas are being treated):
  - Brain injury resulting in loss of strength, sensation or thinking ability
  - Spinal cord injury resulting in paraplegia
  - Lung injury resulting in shortness of breath
  - Esophagus injury resulting in difficulty swallowing
  - Heart injury resulting in a heart attack or fluid collection on the heart
  - Bone injury resulting in a broken bone
  - Rectal or bowel injury resulting in bleeding or perforation (hole) or fistula (abnormal connection between the bowel and another organ)
  - Bladder injury resulting in bleeding or perforation (hole) or fistula (abnormal connection between the bowel and another organ)
  - Adrenal dysfunction resulting in adrenal insufficiency
  - Tissue injury resulting in avascular necrosis

There may or may not be a direct benefit to the patient. The cancer may shrink but these things cannot be predicted. The information learned from this study may or may not help other participants with metastatic cancer and oligo-metastatic disease in the future. The potential benefits of SABR in this setting are that it could reduce side effects and/or improve the chance of controlling the cancer by more accurately treating the cancer and by giving higher doses of radiation.

2.3. Study Population

This study will be offered to patients with up to 5 newly diagnosed or progressing metastatic cancer lesions, meeting all eligibility criteria as described in sections 4.1 and 4.2, respectively.

3. Trial Design

This is a non-randomized phase II trial where all patients will receive experimental SABR for up to 5 newly diagnosed or progressing sites metastatic disease. We will accrue 400 patients to assess toxicity associated with this experimental treatment.

3.1. Study Objectives and Endpoints

3.1.1. Objectives

Primary Objective: To assess quality of life and side effects in patients with up to 5 newly diagnosed or progressing metastatic cancer lesions treated with a comprehensive oligometastatic SABR treatment program.

Secondary Objective: to document disease free and overall survival.

3.1.2. Endpoints

Primary Endpoints

- Patient Reported Outcomes, quality of life and side effects
- Toxicity Assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4

Secondary Endpoints:

- Progression-free survival
- Time from SABR treatment to disease progression at any site or death
- Overall survival
- Lesional control rate, defined as lack of further progression
- Time to starting or re-starting chemotherapy for current cancer
- Number of cycles of further systemic therapy for current cancer

400 patients will be accrued in order to adequately capture these endpoints.

3.2. Entry Procedures

PRE-TREATMENT STAGING/ ASSESSMENTS

Staging/Testing within 14 weeks of patient registration date (no exceptions to timelines)

Imaging/Staging:

- Brain CT or MRI imaging (for tumour sites with propensity for brain metastasis)
- Body imaging:
  - CT neck/chest/abdomen/pelvis, with or without bone scan (at discretion of study doctor), required if no PET-CT is performed
  - PET-CT is only required for specific evidence-based indications, and in such cases the CT neck/chest/abdomen/pelvis and bone scan are not required
  - MRI spine for patients with vertebral or paraspinal metastases

Pre-Tx Simulation Imaging

- 4DCT should be acquired for moving tumours.
- If 4DCT is not possible, 3DCT is acceptable.
- Planning CT slice thickness <= 2.5 mm. (exception: spine SABR – slice thickness = 1.25 mm)
- Intravenous contrast could be used at the discretion of the treating radiation oncologist.
- Fiducial markers could be used at the discretion of the treating radiation oncologist.

Prescription Isodose

- PTV: V100% = 95%
- PTV: V 90% > 99%

Treatment Volumes

- GTV= gross disease on CT, MRI, or PET/CT
- CTV not generally used. Exceptions: 1) liver = GTV + 5mm 2) spine per provincial SABR spine protocol
- PTV= GTV (or CTV where applicable) + 2-5 mm; 2 mm for spinal and brain tumours, 5 mm for all other sites

Testing:

- Pulmonary function tests for lung metastases, if previously documented poor lung function, treating near lung, and at discretion of investigator
- Liver function tests for liver metastases, if previously documented if poor liver function, treating near liver, and at discretion of investigator
- Blood tests as per standard of care
- Urine pregnancy test for women of child-bearing age **within 4 weeks prior to RT start date**

Assessments

- Eligibility Assessment (inclusion/exclusion criteria [see Eligibility Checklist – Appendix A])

- Oligometastases Entry/Registration Form
  - ECOG Status
  - Number of total metastases (max 5)
  - Documentation of site(s) of disease
  - Prior Chemotherapy history documented
  - Able to treat all active sites with ablative intent
- Concomitant medications
- Quality Assurance Review of Contours (SABR Quality Assurance Review)
- Quality of Life POSI Questionnaires (Appendix B)-POSI questionnaires -should be completed before treatment (ex. at time of patient registration or at CT-Simulation)
- Provider Reported Toxicity, Grade 2 or higher, as per CTCAE v.4

a) Randomization

N/A

b) Blinded/Unblinded

N/A

3.3. Study Duration

Anticipated length of study is 8 years. Anticipated end date for recruitment: 30 June 2020. Anticipated end date for completion of all follow-up activities: 30 September 2025

4. Eligibility

Treatment will be offered to patients with up to 5 newly diagnosed or progressing metastatic cancer lesions meeting inclusion and exclusion criteria

Waivers to eligibility criteria are not permitted.

See Eligibility Checklist (Appendix A)

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in this study:

- Age 18 or older
- Able to provide informed consent
- Histologically confirmed malignancy with metastatic disease detected on imaging.
  - Biopsy of metastasis is preferred, but not required.
- Primary tumour treated radically or controlled by prior palliative radiotherapy or systemic therapy
- Maximum 5 metastases eligible for SABR (either 5 in total or 5 not controlled by prior treatment)
- Standard of care tests prior to SABR CT simulation within 14 weeks:
  - Brain CT or MRI imaging (for tumour sites with propensity for brain metastasis)
  - Body imaging:
    - CT chest/abdomen/pelvis, with or without bone scan (at discretion of study doctor), required if no PET-CT is performed
    - PET-CT or PSMA-PET is only required for specific evidence-based indications, and in such cases the CT neck/chest/abdomen/pelvis and bone scan are not required:
    - MRI spine for patients with vertebral or paraspinal metastases
  - For other indications, at the discretion of the treating oncologists, e.g. PET-CT scans may be done but are not required.
  - Blood tests as per standard of care
  - Pregnancy test for women of child-bearing age
- ECOG performance status 0-2
- All sites of progressive disease can be safely treated based on criteria below
- For non-brainstem mets, maximum size of 3cm if using single fraction radiosurgery.
  - If size is from 3.1 to 4cm, 25-35Gy/5 can be considered
- All brain metastases cases need approval from Stereotactic Radiosurgery (SRS) rounds
  - Maximum size of 6 cm for lesions outside the brain, except:
    - Bone metastases over 6 cm may be included, if in the opinion of the local PI it can be treated safely (e.g. rib, scapula, pelvis)
- Life expectancy > 6 months

  - In many scenarios, this is best estimated by a multidisciplinary opinion from disease site experts, often obtained by presentation at multidisciplinary tumours rounds.
- Not a candidate for surgical resection at all sites: surgery to all sites not recommended by multidisciplinary team, or unfit or declining surgery.
- No chemotherapy agents (cytotoxic, or molecularly targeted agents) will be used within the period of time commencing 2 weeks prior to radiation, lasting until 1 week after the last fraction. Certain chemotherapy agents may require a longer break prior to or after SABR if protocols dictate. Hormonal therapy during SABR is allowed.
- Patients with metastases that have been previously treated may be eligible for this SABR protocol:
  - If the previous treatment was systemic therapy, the patient may be eligible, if the metastases have demonstrated a complete radiologic response
  - If the previous treatment was by a local non-radiation means (e.g. prior resection, RFA or microwave ablation), then SABR may be considered for residual/recurrent disease
  - If the previous treatment was SABR, the **patient is not eligible** unless the new site(s) was/were not previously treated
- If the previous treatment was conventional RT, SABR could be considered if it can be delivered safely. In such a circumstance it **must** be presented in a multidisciplinary setting for approval.
- Review and consensus by 3 disease site experts, or tumour group conference, for eligibility/prognosis

  Patients must be able and willing to complete quality of life questionnaires in English, and other assessments that are a part of this study, via paper or online using REDCap (if email address is provided by participant on the informed consent)

Note: The potential treating SABR radiation oncologist reserves the right to require a multidisciplinary note documenting life expectancy, other treatment options and suitability for SABR.

4.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

- Serious medical co-morbidities precluding radiotherapy
- Bone metastasis in a femoral bone if risk of pending fracture is high
- Patients with 1-3 brain metastasis and no disease elsewhere (these patients should not be accrued but treated with stereotactic radiotherapy as per results of published randomized trials)
- Complete response to first-line chemotherapy (i.e. no measurable target for SABR)
- Persistent malignant pleural effusion
- Inability to treat all sites of progressing disease with ablative intent
- Clinical or radiological evidence of spinal cord compression
- Dominant brain metastasis requiring surgical decompression

- A candidate for an open randomized clinical trial comparing SABR to a standard treatment
- Pregnant or lactating women

4.3. Subject Withdrawal Criteria

Subjects may voluntarily discontinue participation in the study at any time.

If a subject is withdrawn from the study, the assessments and evaluations that would have been performed at the Study Completion/Early Termination (see Section 4.8) should be obtained. The Study Termination Form should be completed in REDCap.

Subjects withdrawn or discontinued can be replaced at the discretion of the sponsor-investigator/Study Principal Investigator. Subjects can be withdrawn from the study at the instigation of the investigator if exclusion/inclusion criteria have been violated during the course of treatment ex. Disease progression does not allow for safe treatment of metastatic sites; safety reasons etc.

If a subject is removed because of an adverse or serious event, they should remain under medical observation as long as deemed appropriate by the treating physician, and follow recording and reporting requirements listed in Section 8.2.

4.3.1. Informed Consent

Voluntary, written, dated and signed informed consent for participation in the study must be obtained prior to performing any study-related procedures (including screening evaluations).

The written informed consent form must be approved by the IRB/REB and adhere to ICH GCP and the ethical principles that have their origin in the Declaration of Helsinki.

The investigator is responsible for obtaining written informed consent from each subject, or if the subject is unable to provide informed consent, the subject's legally acceptable representative, prior to beginning any study procedures and treatment(s). The investigator should inform the subject, or the subject's legally acceptable representative, of all aspects of the study, including the potential risks and benefits involved. The potential risks and benefits are described in section 2.2.1 and in the ICF.

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria prior to study enrollment. A screening log will be maintained to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The subject should be given ample time and opportunity to ask questions prior to deciding about participating in the study and be informed that participation in the study is voluntary and that

they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The informed consent must be signed and dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form should be given to the subject or the subject's legally acceptable representative. The process of obtaining informed consent should be documented in the patient source documents. **See Section 12.1.3 for detailed information on informed consent process and documentation.**

4.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened Subjects should be assigned the same subject number as for the initial screening.

4.5. Availability for follow up

Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients on this trial will be available for complete documentation of treatment, adverse events, and follow-up.

4.6. Ability to tolerate current treatment

Patient must be able to maintain a stable position during therapy and be able to tolerate immobilization device(s) that may be required to deliver SABR safely.

Review and consensus must be made by 3 disease site experts, or tumour group conference, for eligibility/prognosis (including patient's ability to tolerate SABR).

4.7. Biopsy/Tissue/Blood banking

As per the eligibility criteria, a biopsy of metastasis is preferred, but not required.

4.8. Schedule of Activities (revise schedule as needed)

4.8.1. Investigations Prior to Randomization/Study Entry, During Trial and Follow-up

Assessment	Screening/ Baseline Staging Investigations	Enrollment/ Randomization	Treatment	Follow-Up Week 6 -3 Month+/- 3 Weeks)	Follow-Up 6 Month (+/- 8 weeks)	Follow-Up every 6 months [12-month, 18-month, 24-month, 30-month, 36-month, 42-month, 48-month, 54-month] (+/- 8 weeks)	Follow-up: 60 Month (+/- 8 weeks) or Early Termination
Informed Consent Form	X						
Inclusion/Exclusion Criteria	X						
Medical History	X			X	X	X	X
Physical Examination	X						
CT scans or MRI scan, or full body CT scan/ PET scan or PSMA PET	X			X ^^	X ^^	X ^^	X ^^
Bone Scan or PET-CT scan (or PET-PSMA for prostate cancer*)	X			Optional	Optional	Optional	Optional
Hematology (PFTs LFTs if applicable)	X						
Pregnancy Test (Urinalysis)	X						
Enrollment		X					
Concomitant Medications	X	X	X	X	X	X	X
Quality of Life Questionnaires (POSI)		X		X	X	X	X
Planning CT		X					
Quality Assurance Review of Contours		X					
SABR Treatment			X				

Assessment	Screening/ Baseline Staging Investigations	Enrollment/ Randomization	Treatment	Follow-Up Week 6 -3 Month+/- 3 Weeks)	Follow-Up 6 Month (+/- 8 weeks)	Follow-Up every 6 months [12-month, 18-month, 24-month, 30-month, 36-month, 42-month, 48-month, 54-month] (+/- 8 weeks)	Follow-up: 60 Month (+/- 8 weeks) or Early Termination
Toxicity Assessment (HCP-reported FU form)				X	X	X	X
Adverse Events			X	X	X	X	X

*Extra imaging outside of study schedule is allowed per discretion of the study doctor

**Imaging is optional for prostate cancer patients with PSA < 5 and is up to the discretion of the treating Radiation Oncologist. If patient develops disease progression, imaging will be per standard of care.

***Follow-up appointments starting at week 6 post-treatment are with the study doctor, (or family doctor if appointment is over videolink/ phone and is requested by study doctor) and questionnaire is completed.

^^ +/- PET, bone scan as clinically indicated; CT Head – Optional

Imaging/Staging:

- Brain CT or MRI imaging (for tumour sites with propensity for brain metastasis)
- Body imaging:
  - CT neck/chest/abdomen/pelvis, with or without bone scan (at discretion of study doctor), required if no PET-CT is performed
  - PET-CT is only required for specific evidence-based indications, and in such cases the CT neck/chest/abdomen/pelvis and bone scan are not required

MRI spine for patients with vertebral or paraspinal metastases

Imaging and blood test results will be valid for 14 weeks prior to enrollment/registration.

Pregnancy test results will be valid for 4 weeks prior to treatment.

Since many patients will be receiving systemic therapy and separately-timed imaging may be required to assess response, attempts should be made to avoid duplication of scans. The follow-up imaging requirements herein **may be adjusted by +/- 8 weeks, from target follow-up date, in order to align with scans** used to assess response to systemic therapy.

5. Subject Treatment Plan

5.1. Trial Treatment Summary

5.1.1. Stereotactic Ablative Radiotherapy

Treatment Planning

Dose / Fractionation / Prescription

PTV: V100% = 95% (The Volume of the PTV receiving 100% of the prescription dose is equal to 95%)
PTV: V 90% > 99% (The Volume of the PTV receiving 90% of the prescription dose is greater than 99%)

PTV coverage is secondary to organs at risk (OAR) constraints based on clinical judgement. PTV coverage can be decreased in order to meet OAR constraints. If the PTV coverage by 100% is <50% of the PTV volume, then patients will not be included in the study. Minimum dose to PTV should be >50% of prescribed dose.

Dose and Fractionation: Location	Dose (Gy)	Fractions	Frequency
Peripheral Lung	48 [54]*	4 [3]*	Daily or every other day
Central Lung - within 2cm of PBT	60	8	daily
Spine (primary)	24 [35]*	2 [5]*	daily
Spine (retreatment)	35 [24]*	5 [2]*	daily
Bone (non-spine)	35 or 24	5 or 2	daily
Liver	54	3	Every other day
Adrenal	40 or 60	5 or 8	daily
LN/Soft Tissue	40	5	daily
Brain	BC Cancer Stereotactic radiosurgery protocol		

***preferred dose or fractionation listed first, while dose or fractions in [square brackets] are the secondary option.**

Immobilization

- Immobilization devices need to be approved by the practicing Radiation Oncologist(s) and SABR physics and dosimetry staff within the particular institution.
- It is left at the discretion of the treating Radiation Oncologist/Medical Physicist to determine which immobilization device is to be used based on their centre/department specific policy.

Pre-Treatment Simulation

- 4D CT should be acquired for tumours which are likely to move from respiratory motion, such and lung, liver and adrenal sites.
- If 4DCT is not possible, 3DCT is acceptable
- Planning CT slice thickness: CT slices thickness should be no greater than 3mm, and pixel sizes should be no greater than 1x1 mm. For Spine SABR, the CT slice thickness should be no greater than 2 mm (e.g. 1.25 mm)
- Intravenous contrast may be used at the discretion of the treating Radiation Oncologist.
- Fiducial markers may be used at the discretion of the treating Radiation Oncologist.
- When available, 4DCT images should be sent to Treatment Planning System:
  - All phases 0 – 90
  - MIP (Maximum Intensity Projection)
  - MIN (Minimum Intensity: for bony lesions)
  - Average CT (if used for planning purposes)

Treatment Volumes

For all lesions, the gross tumour volume (GTV) will be defined as the visible tumour on CT and/or MRI imaging. When used for target definition, MRI and/or PET imaging should be registered with the planning CT

For mobile lesions (e.g. Lung and Liver tumours) an internal GTV (IGTV) can be created as per site specific BC Cancer clinical protocols.

A Clinical Target Volume (CTV) in general will not be used, except in liver and bone. For vertebral lesions, the CTV will be as per the BC Cancer spine SABR protocol. For bone, a CTV of 5 mm is optional.

A PTV margin of 2-5 mm will be added depending on site of disease and local immobilization and image guidance practices: no less than a 2 mm margins may be used for spinal stereotactic treatments, 2 mm for brain tumours, and no less than a 5 mm margin for other sites. For radiosurgery platforms, a PTV margin of 0-1 mm is permitted. In situations where imaging or immobilization may be limited, > 5 mm margins may be considered for non-spinal bone metastases.

Organs at risk visible in the planning CT scan (**Appendix D**) will be contoured.

For spinal lesions, a pre-treatment MRI is required to assess the extent of disease and position of the cord. This must be fused with the planning CT scan. A Planning Organ at Risk Volume (PRV) expansion of no less than 2 mm will be added to the spinal cord, and dose constraints for the spinal cord apply to this PRV. For radiosurgery platforms, a PRV margin of 1 mm is permitted for the spinal cord.

Relevant Organs at Risk (OAR)

- The relevant OARs are dependent on the location of the target volume and should be outlined from the simulation CT.
- As a general rule, critical structures **within 5 cm of the PTV** should be contoured.
- Please refer to **Appendix D** for a list of structures that should be considered for different treatment sites.

Treatment Planning / Technique

Technique

- 3DCRT or IMRT/VMAT delivery techniques are allowed.
- 6MV megavoltage beams and 6 or 10 MV Flattening Filter Free (FFF) beams may be used. FFF beams are encouraged due to their high dose rate.

Dose Calculation Algorithm:

- Type II only (3D scatter correction dose algorithms, such as Eclipse AAA, Acuros, or Collapsed Cone)
- Inhomogeneity Corrections = ON
- Dose grid resolution should be approximately equal to the CT slice thickness, and no larger than 3mm with a higher resolution for Spine SABR

PTV Prescription isodose:

- The Volume of the PTV receiving 100% of the prescription dose is equal to 95% while the Volume of the PTV receiving 90% of the prescription dose is greater than 99%.
- PTV coverage may be compromised to achieve dose constraints for critical OARs at the discretion of the Radiation Oncologist, but PTV coverage must be such that 50% isodose covers 95% of the PTV (V50%> 99%).
- Chest wall dose constraints can be exceeded in order to meet PTV coverage, at the discretion of the treating oncologist.
- The hotspot should be in the PTV and not in the adjacent normal tissue. The hotspot should generally be less than 150% of the prescription dose. For lung lesions, the hotspot should not exceed 167% of the prescription dose.

OAR and Normal Tissue Dose Constraints:

- Please refer to **Appendix D** for the OAR dose constraints.
- The dose distribution should conform to the PTV as much as possible. As a guideline for a single lung lesion, please refer to **Appendix D** for dose conformality indices. For multiple lung lesions, the specified dose conformality indices might not be achievable.

Treatment Verification / Imaging

- Collision Check: Recommended for all plans containing non-coplanar beams
- KV, MV or CBCT image guidance must be used for all fractions. It is strongly recommended that CBCT Image Guidance is used for all treatment fractions as indicated in the following table:

Verification Imaging	Frequency	Purpose
Pre-Tx CBCT	Daily	Move to match
Post-Tx CBCT	Day 1 or at RO discretion	Assess intra-fraction movement

- If treatment time is expected to exceed 45 minutes, mid-tx position verification should be performed.

Quality Assurance

The contours of the GTV, IGTV, PTV and all relevant OAR will be evaluated and approved upon review by a second Radiation Oncologist (See Quality Assurance (QA) forms. ***E-approval is acceptable if all elements on QA forms are addressed in e-communications, including final approval of contours***).

- Dose volume histogram parameters will be evaluated by the planning dosimetrist(s), physicist(s) and Radiation Oncologist(s).

- Institutional quality assurance rounds may also evaluate the radiation plans and delivery of oligometastases SABR.

- All plans must be independently verified with measurements and/or with quality assurance software used in the verification of SABR plans.

5.2. Data Handling and Recordkeeping

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, REB review, and regulatory agency inspections and provide direct access to source data documents.

- The Sponsor-Investigator/Study PI or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor-Investigator/Study PI assumes accountability for actions delegated to other individuals
- Study monitor will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of Subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion. No records may be destroyed during the trial and/or retention period. No records may be transferred to another location or party without written notification to the sponsor.

5.3. Lifestyle Considerations, Prohibited Food and Additional Restrictions

5.3.1. Required Therapy

None

5.3.2. Permitted Concomitant Therapy

All cancer-specific concomitant medications that the subject is using should be recorded at each visit.

Previous systemic, radiation, and hormone therapy is permitted. Hormone therapy is allowed during treatment. All concomitant medications should be continued throughout the trial unless the responsible investigator (ie. Treating Radiation Oncologist) decides otherwise.

5.3.3. Prohibited Concomitant Therapy

Use of the following concomitant therapies is prohibited as described below:

- The use of systemic therapy agents that are cytotoxic, immunotherapeutic, or molecularly targeted agents are NOT allowed within the period of time commencing 2 weeks prior to radiation, lasting until 1 week after the last fraction.

Use of chemotherapy schemes containing potent enhancers of radiation damage (e.g. gemcitabine, doxorubicin, bevacizumab, adriamycin) are discouraged within the first month after radiation.

5.3.4. Herbal Therapies

Concomitant herbal therapies that the subject is using do not need to be recorded.

5.3.5. Data Records for Concomitant Medications

Cancer-specific concomitant medications must be recorded on the **SABR-5 concomitant medication form**, which is a cumulative form to be updated throughout the study.

If no concomitant medications are being taken at the time of study visits, this can be indicated on a line on the form, with the following annotation:

'Confirmed no concomitant medications are being taken during study visit X [Date: DD MMM YYYY; INITIALS]'

5.4. Co-enrolment

Enrolment in other studies **may** be permitted. Investigators **must** check with the Study Principal Investigator.

5.5. Subject Compliance/Deviations

Subject compliance, such as attending study visits and completing questionnaires, will be monitored via REDCap. If any visits are not completed, investigator or delegate must call and conduct follow-up over the telephone, or send questionnaires to patients via regular mail, to complete POSI questionnaires, and the HCP form for outcomes and toxicity. Missed visits must be documented in the deviation log.

Deviations to eliminate immediate hazards to study subjects must be reported to the Study PI immediately upon discovery and to the REB within 7 calendar days. All other reportable deviations must be reported to the Study PI immediately, however to the REB within 15 calendar days. See section **12.1.2 Protocol Deviations** for a list of deviations.

6. Dose Modifications

6.1. General Toxicity Management

Dose modifications are not allowed; but PTV undercoverage is allowed and already described.

6.2. Treatment Modifications

Interruptions and missed doses are major deviations and must be recorded in the deviation log on paper and in REDCap. Major deviations must be reported to the Study PI immediately and may require an additional deviation report (see Section 12.1.2).

7. Assessment of Efficacy

Assessment of Response and Patient Follow-Up

7.1. Schedule

Clinical follow-up appointments will occur at 6 weeks-3 months, and then every 6 months (from treatment end date) for 5 years. At each visit, a medical history including an examination of concurrent medication will be conducted by the oncologist or a delegated family physician (e.g. if patient is followed over videolink), and CTC-AE toxicities recorded. Quality of life questionnaires are to be completed at each visit and can be done remotely if needed (e.g. by phone, videolink, or mail), or the patient can complete these questionnaires at home (paper and mailed to investigator) or online using REDCap

CT head (or MR head), CT chest, abdomen and pelvis, and bone scans will be repeated every 6 months, (+/- PET-CT, bone scan as clinically indicated) until 5 years have elapsed. Head imaging can be omitted for histologies without a propensity for brain metastases (e.g. prostate). PET-CT scanning may be used in follow-up for patients who were staged with a PET-CT scan for trial entry. In such cases, the PET-CT replaces the CTs of the chest, abdomen, pelvis and the bone scan; brain imaging would still be required for histologies (definition of propensity for brain metastases to be left to the treating investigator) with a propensity for brain metastases. *Extra imaging outside of study schedule is allowed per discretion of the study doctor. ***Patients with prostate cancer who have a PSA below 5 may omit imaging requirements.***

Since many patients will be receiving systemic therapy and separately-timed imaging may be required to assess response, attempts should be made to avoid duplication of scans. ***The imaging requirements herein may be adjusted by +/- 8 weeks, from target follow-up date, in order to align with scans used to assess response to systemic therapy.***

7.2 Patient Reported Outcomes

See **Appendix B**

Patient Reported Outcomes will be collected using the questionnaires chosen for BC Cancer's Prospective Outcomes and Support Initiative (POSI: H14-00647) based on body site being treated (see Appendix B).

7.3 Physician/RN/Other Reported Outcomes

See **HCP-Reported Follow-Up (Outcomes and Toxicity)**

- ECOG performance status
- Outcomes including recurrence, therapy since SABR, and toxicity

- Next local therapy or chemotherapy/ targeted therapy start date
- Date of relapse or new metastases
- Date of Death
- CTCAE version 4.0 toxicity

7.4 Measurement of Response

- Survival outcomes: Overall survival will be measured as time until death from any cause, and progression-free survival as time to either progression or death, whichever occurs first.
- Lesion control rate will be assessed retrospectively as RECIST criteria have not been validated in the setting of SABR, and is costly to implement in a prospective cohort

8. Assessment of Safety

8.1. Specification of Safety Parameters

STUDY ENDPOINTS AND STOPPING RULES

The primary objective of this study is to measure quality of life and side effects (as determined by toxicity) associated with SABR. Thus, the larger the sample size the more confident we can be that adverse events are not common with SABR as prescribed and delivered on this protocol. We initially set the sample size at 200, but since accrual has been successful, and in order to have more confidence in the safety of SABR, we are doubling the sample size to 400. In addition, lymph node treatment with SABR is a particular interest, and thus increasing the sample size in order to accrue 50 patients will give us more confidence in a less than 10% incidence of grade 4 toxicity (see below). Increasing the sample size to 400 patients gives us a 66% chance to accrue over 50 lymph node metastases, while increasing the sample size to 300 only gives us a <20% chance of accruing over 50 such patients.

This study with an original sample size of 200 patients had limited power to detect an increased incidence of adverse events and complicates (see Tables below). For this reason, the trial's power is augmented by aSABR-5 Toxicity Committee), which is bound by rules that require the suspension/termination of a trial accrual under certain events as outlined below.

Probabilities for exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 5%, 4%, 3%, 2%, assuming sample size of 100

# of grade 4 toxicity events out of 100 samples	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 5%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 4%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 3%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 2%
0	0.6%	1.7%	4.8%	13.3%
1	3.1%	7%	14.7%	27.1%
2	8.1%	14.5%	22.5%	27.3%
3	14%	19.7%	22.7%	18.2%
4	17.8%	20%	17.1%	9%
5	18%	16%	10.1%	3.5%
6	15%	10.5%	5%	1.1%

Probabilities for exact # of grade 4 toxicity events given true rate of grade 4 toxicities =5%, 4%, 3%, 2% for a sample size = 200

# of grade 4 toxicity events out of a sample size =200	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 5%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 4%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 3%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 2%
0	0.004%	0.03%	0.2%	1.8%
1	0.04%	0.2%	1.4%	7.2%
2	0.2%	1%	4.3%	14.6%
3	0.7%	2.7%	8.8%	19.6%
4	1.7%	5.6%	13.4%	19.7%
5	3.6%	9.1%	16.2%	15.8%
6	6.1%	12.3%	16.3%	10.5%

95% confidence interval for true rate of toxicities with sample size = 100 or 200

# of grade 4 toxicity events	Upper limits of one-sided 95% confidence interval for true rate of grade 4 toxicities (sample size=100)	Upper limits of one-sided 95% confidence interval for true rate of grade 4 toxicities (sample size=200)
0	3%	1.5%
1	4.7%	2.3%
2	6.2%	3.1%
3	7.6%	3.8%
4	8.9%	4.5%
5	10.2%	5.2%
6	11.5%	5.8%

Additional Tables with sample size increase to 400:

Probabilities for exact # of grade 4 toxicity events given true rate of grade 4 toxicities =5%, 4%, 3%, 2% for a sample size = 400

# of grade 4 toxicity events out of a sample size =400	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 5%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 4%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 3%	Probability of exact # of grade 4 toxicity events given true rate of grade 4 toxicities = 2%
0	0.00000012%	0.0000081%	0.00051%	0.031%
1	0.0000026%	0.00014%	0.0063%	0.25%
2	0.000027%	0.0011%	0.039%	1.03%
3	0.00019%	0.0062%	0.16%	2.8%
4	0.0010%	0.026%	0.49%	5.6%
5	0.0041%	0.085%	1.20%	9.1%
6	0.014%	0.23%	2.45%	12%

Cumulative Probabilities grade 4 toxicity events given true rate of grade 4 toxicities =5%, 4%, 3%, 2% for a sample size = 400

# of grade 4 toxicity events out of a sample size =400	true rate of grade 4 toxicities = 5%	true rate of grade 4 toxicities = 4%	true rate of grade 4 toxicities = 3%	true rate of grade 4 toxicities = 2%
<=0	0.00000012%	0.0000081%	0.00051%	0.031%
<=1	0.0000027%	0.00014%	0.0068%	0.28%
<=2	0.000030%	0.0013%	0.046%	1.3%
<=3	0.00022%	0.0075%	0.21%	4.1%
<=4	0.0012%	0.033%	0.70%	9.7%
<=5	0.0053%	0.12%	1.9%	19%
<=6	0.020%	0.35%	4.4%	31%

95% one-sided confidence interval for true rate of grade 4 toxicities with sample size =400, 50

# of grade 4 toxicity events	Upper limits of one-sided 95% confidence interval for true rate of grade 4 toxicities (sample size=400)	Upper limits of one-sided 95% confidence interval for true rate of grade 4 toxicities (sample size=50)
0	0.75%	5.8%
1	1.2%	9.1%
2	1.6%	12%
3	1.9%	15%
4	2.3%	17%
5	2.6%	20%
6	2.9%	22%

The last table above also demonstrates our confidence of grade 4 toxicities within smaller subsets of SABR patients receiving lymph node SABR. With our larger sample size of 400, there is a 66% chance we will accrue 50 lymph node metastases (based on the fact that we accrued 20 in the first 150 patients); if we detect 0 or 1 grade 4 toxicities, that will be associated with a 95% confidence that the true rate of grade 4 toxicity is below 10%.

The primary objective of this study is to assess quality of life and toxicity post SABR for oligometastases. If any grade 5 SAEs definitely, probably, or possibly related to protocol treatment occur, all co-investigators at each site will be made aware within 1 week of reporting to the principal investigator (PI), and a SABR-5 Toxicity Committee meeting will be held within one month of the event. During this time, any other patients on treatment to the same body site where the grade 5 toxicity was interpreted to originate (e.g. adrenal metastases) will have their

plan reviewed by the PI to determine if that patients' treatment should be put on hold prior to SABR-5 Toxicity meeting.

If 3 or more grade 5 SAEs meet the definition of unanticipated problem (i.e. unexpected, related and involving greater risk occur during this study), the study will be temporarily put on hold in order to organize a SABR-5 Toxicity Committee meeting and initiate conversations with the BC Cancer/UBC REB. Depending on the results of these meetings the study may be permanently closed or significant modifications may be made and re-reviewed by the REB (e.g. remove treatments of adrenal metastases from the study, or reducing the dose, if toxicity was from this body part treatment with SABR).

For the purpose of reporting this study, we will define SABR for oligometatases to be reasonably safe with the following a priori endpoints. We will report the 95% confidence interval (see table above) that the upper confidence is equal to or lower than. In other words, 4 toxicities (with sample size of 200) we have 95% confidence the toxicity (whatever grade) is <5% or lower. Likewise, with 6 toxicities, we have 95% confidence the toxicity is less than 6%.

- <5% grade 5 toxicity
- <10% grade 4 toxicity
- < 25% grade 3 toxicity

8.2. Recording and Reporting of Adverse Events

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue study treatment or participation in the study.

8.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the start of RT treatment until completion of all follow-up visits.

All SAEs will be collected from the start of RT treatment until completion of all follow-up visits.

Medical occurrences that begin before the start of study RT treatment but after obtaining informed consent will be recorded in the subject's medical record.

8.2.2. Method of Detecting AEs and SAEs

Definitions

Adverse Event (AE) is 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.

Serious Adverse Event (SAE) as defined in the ICH Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, E2A Section IIB includes any untoward medical occurrence that at any dose:

- Results in death*
- Is life-threatening (refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly/birth defect

*underlying cause of death must be investigated and confirmed by the PI to be reported as an SAE. If death is due to disease progression, this is reported using the **Study Termination Form** in REDCap. Deaths from disease progression are not to be recorded as SAEs.

Important medical events that may not be immediately life-threatening or result in death or hospitalization may be considered a serious adverse event, when, based upon medical and scientific judgment, they may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Causality (attribution)

An adverse event is considered **related** to the research intervention if there is a reasonable possibility that the event may have been caused by the research intervention (i.e. a causal relationship between the event and the research intervention cannot be ruled out by the investigator(s)). The relationship of an AE to the study treatment (causality) will be described using the following definitions:

Unrelated: Any adverse event for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study treatment and the adverse event does not follow any previously documented pattern.

The adverse event, after careful consideration by the investigator, is clearly and incontrovertibly due to causes other than the intervention.

Unlikely: Any adverse event for which the time relationship between the study treatment and the event suggests that a causal relationship is unlikely and/or the event is more likely due to the subject's clinical condition or other therapies concomitantly administered to the subject.

Possible: Any adverse event occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The adverse event, after careful consideration by the investigator, is considered to be unlikely related but cannot be ruled out with certainty.

Probable: Any adverse event occurring in a timely manner after the administration of the study treatment that follows a known pattern to the intervention and for which no other explanation is known. The adverse event, after careful consideration by the investigator, is believed with a high degree of certainty to be related to the intervention.

Definitely Related: Any adverse event occurring within a timely manner after administration of the study treatment that is a known sequela of the intervention and follows a previously documented pattern but for which no other explanation is known. The adverse event is believed by the investigator to be incontrovertibly related to the intervention.

Severity

The severity of adverse events will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading scale (see (http://ctep.cancer.gov).

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life-threatening or disabling
Grade 5: Death

Note: The term "severe" is a measure of intensity: thus a severe adverse event is not necessarily **serious**. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Grade 1 toxicities such as mild fatigue, nausea, vomiting, skin irritation, pain, loss of appetite and some physical function are common and expected side effects of radiation therapy and therefore should not be reported as adverse events if the event is documented in the subject's medical record[15].

Only Grade 2 or higher toxicities that are possibly, probably, or definitely related to SABR treatment will be documented and reported as AEs/SAEs.

These toxicities must be documented in the AE log and SAE report form, and entered in REDCap, and follow REB and BC Cancer reporting guidelines.

Immediately Reportable Adverse Events

Any **Grade 4 or 5 serious adverse event** that is definitely, probably, or possibly the result of protocol treatment must be reported to the Study PI within 24 hours of discovery. The follow-up/final report should be completed within an additional 8 days. All other SAEs (Grade 2-3) that are definitely, probably, or possibly related to treatment should be reported to the Study PI within 15 days. These should be documented in an SAE Report form and in REDCap as well.

Unanticipated/unexpected events include events that are inconsistent with, or present a greater risk of harm, than the known or recognized risks or side effects of SABR treatment, as described in Section 2.2.1. Unanticipated events also include those events where there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research (i.e. possibly, probably, or definitely related to

participation in the research itself). Unanticipated events are to be reported to the Study PI within 24 hours of discovery, and to the local REB as required.

All local (internal) **serious**, **unexpected** adverse events will be reported to the applicable REB as per their reporting guidelines.

NOTE: Conditions that are NOT considered a SAE in this protocol are not included in reporting requirements, e.g., hospitalizations for routine procedures, disease progression, or death from disease progression.

8.3. Follow-up of Subjects after Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow the subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 11.5).

Dissemination of Safety Events

The Study PI will notify all participating sites of Grade 4 or 5 SAEs (as described above) within 7 days of receipt of the report. Follow up information will be sent as it becomes available. Investigators will review and file these reports in their trial documentation, and submit the reports to their local REBs if required.

8.4. Pregnancy

Details of pregnancy will not be collected.

9.0. Statistics

9.1 Statistical Methods

Primary objective

Quality of life at 6 months will be measured using FACIT, Cancer Specific Questionnaires, with differences between groups tested using the Student's t-test[17]. Differences in rates of grade 2 or higher toxicity between groups will be tested using the Fisher's Exact Test.

Survival Endpoints

PFS and OS will be calculated using the Kaplan-Meier method with differences compared using the stratified log-rank test. A Cox multivariable regression analysis will be used to determine baseline factors predictive of survival endpoints. For the endpoint of time to new metastases, a Fine and Gray competing risk analysis will be used to account for competing risk of death

9.2. Planned Subjects Enrolled

The primary objective of this study is to assess quality of life and determine the toxicity associated with SABR, thus the larger the sample size the more confident we can be that adverse events are not common with SABR as prescribed and delivered on this protocol. We initially set the sample size at 200, but since accrual has been successful, and in order to have more confidence in the safety of SABR, we are doubling the sample size to 400. In addition, lymph node treatment with SABR is a particular interest, and with 20 patients accrued to date, we must increase the sample size in order to accrue 50 patients, which gives us more confidence in a less than 10% incidence of grade 4 toxicity (see below). Increasing the sample size to 400 patients gives us a 66% chance to accrue over 50 lymph node metastases, while increasing the sample size to 300 only gives us a <20% chance of accruing over 50 such patients.

9.3. Procedures for Reporting Deviations from the Statistical Plan

Any deviations from the original statistical plan should be described and justified in progress and/or in the final report, as appropriate.

10. Measurement of Study Endpoints

10.1 Definitions

10.1.1 Survival outcomes

Overall survival will be measured as time until death from any cause, and progression-free survival as time to either progression or death, whichever occurs first.

10.1.2 Lesion control rate

Lesion control rate will be assessed retrospectively as RECIST criteria have not been validated in the setting of SABR, and is costly to implement in a prospective cohort.

10.1.3 Toxicity

Toxicity will be measured using CTCAE v4.0.

10.1.4 Quality of Life

Responses to site-specific POSI questionnaires will be measured before and after treatment.

10.2 Evidence of Disease Recurrence

Disease recurrence/progression will be detected upon imaging, standard of care testing (e.g. biochemical recurrence as evidenced by increases in tumour-specific blood tests past normal values), and/or detected upon clinical examination during follow-up visits. If there is progression outside of a SABR site, and it meets RECIST criteria, this may be considered distant recurrence, however should be reassessed and confirmed in a subsequent scan as scarring around SABR can mimic recurrence.

10.3 Dating of First Recurrence

Date of first recurrence will be the date of the scan showing new or progressive growth of lesion(s), or the date of laboratory tests showing tumour-specific blood tests increased past normal parameters.

Date of first occurrence must be captured on **the HCP-Reported FU form and in REDCap**.

10.4 Management Following Recurrence

Progressive disease
A primary objective of this study is to assess toxicity, specifically Grade 2 or higher toxicity, of SABR used on this study, not overall survival, and therefore strict control of subsequent treatments is outside the mandate of this trial. If patients develop new, untreated metastatic

deposits, treatment decisions are up to treating oncologist within the constraints of provincial and regional guidelines. The subsequent treatment is not mandated by this study, nor are the outcomes recorded for subsequent treatments, but original SABR toxicity on trial should be followed as long as feasible for the patient. Patients could be considered for SABR at subsequent sites, if such deposits, or progression at previously stable sites, can be treated safely with SABR, though ultimately this is a clinical decision outside the mandate of this trial. If SABR is not possible, then palliative RT can be delivered if indicated. If a patient progresses at the same site they were treated with SABR, then they should be treated with standard of care which may involve SABR as long as site can be safely treated, and at the discretion of the treating oncologist within the constraints of provincial and regional clinical treatment guidelines.

Follow-up evaluations and questionnaire completions will still be based on schedule 4.8 for the original SABR treated sites on trial. However, if necessary, it can be changed at study doctor's discretion if the patient is deteriorating and no longer able to complete questionnaires. The questionnaires may be done via mail or telephone call.

11 Discontinuation of Trial and Subject Discontinuation/Withdrawal

11.1 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last subject in the trial globally.

11.2 Discontinuation of trial

If any Grade 5 Serious Adverse Events (SAEs) definitely, probably, or possibly related to protocol treatment occur, all site PIs will be made aware within 1 week of reporting to the Sponsor-Investigator/Study PI), and a Data Safety Monitoring Committee (DSMC) meeting will be held within one month of the event. During this time, any other patients on treatment to the same body site where the Grade 5 toxicity was interpreted to originate, (e.g. adrenal metastases) will have their plan reviewed by the PI to determine if that patients' treatment should be put on hold prior to DSMC meeting.

If 3 or more Grade 5 SAEs meet the definition of unanticipated problem (i.e. unexpected, related and involving greater risk occur during this study), the study will be temporarily put on hold in order to organize a DSMC meeting and initiate conversations with the BC Cancer/UBC REB. Depending on the results of these meetings, the study may be permanently closed or significant modifications may be made and re-reviewed by the REB (e.g. remove treatments of adrenal metastases from the study, or reduce the dose, if toxicity was from this body part treatment with SABR).

11.3 Subject Discontinuation/Withdrawal from the Study

- Subjects may voluntarily discontinue participation in the study at any time. If a subject is removed from the study, the clinical and laboratory evaluations that would have been performed at the end of the study should be obtained. If a subject is removed because of an adverse event, they should remain under medical observation as long as deemed appropriate by the treating physician. A subject may be withdrawn from the study at the investigator's discretion if any exclusion/inclusion criteria have been violated during the study, or for safety reasons, etc.
- At the time of discontinuing from the study, if possible, an early discontinuation/termination visit should be conducted. See Section 4.8 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The date and reason for Subject discontinuation must be recorded on the **Study Termination form in REDCap.**

11.4 Post-Trial Follow-up

There is no planned follow-up at the end of the study. Additional care to be provided to Subjects after they complete or discontinue the study will involve standard of care treatment for what is normally expected for their condition.

11.5 Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

12 Regulatory, Ethical, and Study Oversight Considerations

The Principal Investigator will obtain ethical approval and clinical trial authorization by competent authorities according to local laws and regulations.

12.1 Regulatory and Ethical Considerations

12.1.1 REB (Research Ethics Board) Approvals for Protocols

This study will be conducted in accordance with the protocol and with the following:

- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol (and any amendments), the informed consent form, and any other written information to be given to subjects will be reviewed and approved by a properly constituted Institutional Review Board (IRB)/Research Ethics Board (REB), operating in accordance with, ICH GCP and local regulatory requirements. A letter to the investigator documenting the date of the approval of the protocol and informed consent form will be obtained from the IRB/REB prior to initiating the study.

Site Principal Investigators will be responsible for the following:

- Notifying the REB of SAEs and unanticipated problems or other significant safety findings as required by REB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the REB and all other applicable local regulations

12.1.2 Protocol Deviations

A protocol deviation occurs when the subject, investigator, or staff fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to comply with OAR constraints
- Failure to comply with treatment dose, fractionations, and/or frequency as specified in this protocol
- Failure to conduct study follow-up visits and/or to collect study-related data within the timeframes as specified in this protocol
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Study Principal Investigator will determine if a protocol deviation will result in withdrawal of a subject.

When a protocol deviation occurs, it must be documented on the **Protocol Deviation Log** in REDCap. The deviation will be discussed with the investigator and a **Protocol Deviation**

Report detailing the deviation may be requested. This form will be signed by the Sponsor and the Investigator. The deviation may also require further reporting to the REB.

12.1.3 Informed Consent Process

The investigator is responsible for obtaining written informed consent from each subject, or if the subject is unable to provide informed consent, the subject's legally acceptable representative, prior to beginning any study procedures and treatment(s). The investigator should inform the subject, or the subject's legally acceptable representative, of all aspects of the study, including the potential risks and benefits involved.

The subject should be given ample time and opportunity to ask questions prior to deciding about participating in the study and be informed that participation in the study is voluntary and that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The informed consent must be signed and dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF.

The process of obtaining informed consent must be documented in the subject's source documents.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

12.1.4 Data Protection

Confidentiality of Subject Records

The names and personal information of study participants will be held in strict confidence. All study records (case report forms, safety reports, correspondence, etc.) will only identify the subject by initials and the assigned study identification number. The investigator will maintain a confidential subject identification list (Master List) during the course of the study. Access to confidential information (i.e., source documents and patient records) is only permitted for direct subject management and for those involved in monitoring the conduct of the study (i.e., Sponsors, CROs, auditors, representatives of the IRB/REB, and regulatory agencies). The subject's name will not be used in any public report of the study. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent

12.1.5 Committees Structure

There is no independent Data and Safety Monitoring Committee (DSMC) for this study. The SABR-5 Toxicity Committee will be made up of the study investigators. The committee will meet once or twice annually (as required) after study initiation to review toxicity outcomes. If any grade 3-5 toxicity is reported, the committee will review the case notes to determine if such toxicity is related to treatment. If the committee deems that toxicity rates are excessive (>25% grade 3 toxicity, or >10% grade 4 or >3% 5 toxicity), then the committee can, at its discretion, recommend cessation of the trial, dose adjustment, or exclusion of certain treatment sites that are deemed as high-risk for complications.

12.5 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

BC Cancer reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Study PI or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the REB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of Subjects by the investigator

If the study is prematurely terminated or suspended, the Sponsor-Investigator/Study PI shall promptly inform the Investigators, the REBs, and regulatory authorities as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

12.6 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the Sponsor-Investigator/Study PI to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor-Investigator/Study PI will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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APPENDIX A - ELIGIBILITY CHECKLIST

Eligibility Checklist for Oligometastatic Disease

You must be able to circle Y (**Yes**) or N/A to all of the following:

Y/N: 5 or fewer progressing metastases
Y/N: Age 18 or older
Y/N: Willing to provide informed consent
Y/N: Patient must have histologically confirmed malignancy with a maximum of 5 progressing metastatic deposits on imaging.
Y/N: Not suitable for surgical resection at all sites or decline surgery
Y/N: Patient has had a CT chest abdomen and pelvis or PET-CT
Y/N or N/A: Patient has had a nuclear medicine bone scan (if no PET-CT)
Y/N or N/A: If solitary lung nodule for which biopsy is unsuccessful or not possible, patient has had an FDG PET scan or CT (chest, abdomen, pelvis) and bone scan
Y/N or N/A: If colorectal primary with rising CEA, but equivocal imaging, patient has had an FDG PET scan
Y/N or N/A: Patient has had CT or MRI brain imaging if primary has a propensity for CNS metastases
Y/N or N/A: Patient has had pulmonary function tests if treating lung lesion(s) and at discretion of treating radiation oncologist
Y/N or N/A: Patient has had liver function tests if treating liver lesion(s) and at discretion of treating radiation oncologist
Y/N or N/A: Patient is judged able to:
- Maintain a stable position during therapy
- Tolerate immobilization device(s) that may be required to deliver SABR safely

Y/N or N/A: Negative pregnancy test for women of child-bearing potential within 4 weeks prior to treatment
Y/N: ECOG performance status 0-2
Y/N: Review and consensus by 3 disease site experts, or tumour group conference, for eligibility/prognosis (Brain mets must be reviewed by Stereotactic Radiosurgery (SRS) rounds)
Y/N: Patient is able and willing to complete study questionnaires

Exclusion Criteria

You must be able to circle N (**No**) to all of the following:

Y/N: Previous SABR to the lesion(s)
Y/N: Lesion in a femoral bone requiring surgical fixation
Y/N: Persistent malignant pleural effusion

Y/N: Comorbidities precluding radiotherapy
Y/N: Chemotherapy/systemic therapy within the last 48 hours
Y/N or N/A: Patients with 1-3 brain metastasis and no disease elsewhere (these patients should not be accrued but be treated with stereotactic radiotherapy off trial as per results of randomized trials)
Y/N: Complete response to first-line chemotherapy (i.e. no measurable target for SABR)
Y/N: Inability to treat all sites of progressing malignant disease
Y/N: Clinical or radiologic evidence of spinal cord compression
Y/N: Dominant brain metastasis requiring surgical decompression
Y/N: A candidate for an open clinical trial at treating centre that randomizes between SABR and a standard treatment

APPENDIX B - PATIENT-REPORTED QUALITY OF LIFE – POSI

Bone metastases: POSI Brief Pain Inventory questionnaire

Brain metastases: POSI CNS questionnaire

Head & Neck metastases: POSI HN questionnaire, which includes MDASI-HN

Lung metastases: POSI SABR Lung questionnaire, which include the FACT FLSI-12

Abdominal/Adrenal metastases: FACIT AD Version 4

Male Pelvis: SHIM and IPSS questionnaires

Female Pelvis: POSI gyne questionnaire, which includes the EPIC Bowel 2, EPIC Urinary 2, PRO-CTAE GI Toxicity, EORTC QLQ CX-24, and EQ5DL

APPENDIX C - RADIATION VOLUMES and DOSES

For all lesions, the gross tumour volume (GTV) will be defined as the visible tumour on CT and/or MRI imaging +/- PET.

- CTV will be added at the discretion of the MRP but in general not needed except in liver (~5mm) and spine.

For vertebral lesions, the CTV will be as practice per spine SABR protocol. A Planning Target Volume (PTV) margin of 2-5 mm will be added depending on site of disease, immobilization, and institutional set-up accuracy: 2 mm margins may be used for spinal stereotactic treatments, 2 mm for brain tumours, and 5 mm for other sites. In situations where imaging or immobilization may be limited, > 5 mm margins may be considered for non-spinal bone metastases.

Organs at risk visible in the planning CT scan (Appendix D) will be contoured. For radiosurgery platforms, a PTV margin of 0-1 mm is permitted.

For spinal lesions, a pre-treatment MRI is required to assess the extent of disease and position of the cord. This must be fused with the planning CT scan. A Planning Organ at Risk Volume (PRV) expansion of 2 mm will be added to the spinal cord, and dose constraints for the spinal cord apply to this PRV. For radiosurgery platforms, a PRV margin of 1 mm is permitted for the spinal cord.

APPENDIX D- SABR ORGAN-AT-RISK (OAR) CONSTRAINTS

Dose constraints

These are based on the AAPM TG 101, SABR-COMET, SC-24 trials as well as most updated references. If any structure is not listed, the constraints may be calculated using the linear quadratic formula from accepted QUANTEC doses, using an alpha-beta ratio of 3 (except neural structure: alpha-beta of 2) for late effects.

Table 1. Dose and fractionations by site with [secondary options in square brackets]

OAR	SABR ORGAN-AT-RISK (OAR) CONSTRAINTS				
	Dmax to ≤=0.035cc for all OARs. Exception: Dmax to 0cc (hard max) → Spinal cord, Spinal cord PRV, Thecal sac/Cauda Equina				
	Fractions				
	2 (for spine mets only as per CCTG SC24)	**3**	**4**	**5**	**8**
Spinal Cord PRV (2mm on cord) (or Spinal Canal)	Dmax ≤ 17 Gy[12]	Dmax ≤ 20.3 Gy[13]	Dmax ≤ 23 Gy [13]	Dmax ≤ 25.3 Gy [13]	Dmax ≤ 30.6 Gy[13]
Spinal Cord PRV /Thecal Sac (reirradiation)	See Table 6 below[11] (NB: 1st row with 0 nBED not applicable, see above for 1st time spine treatment)				
Thecal Sac / Cauda equina	Dmax ≤ 17 Gy[12]	Dmax ≤ 24 Gy[1] V21.9 Gy ≤ 5 cc[1]	D_{max} ≤ 29 Gy [1*] V27 Gy ≤ 5 cc[1*]	Dmax ≤ 32 Gy[1] V30 Gy ≤ 5 cc[1]	Dmax ≤ 39 Gy[1*] V36 Gy ≤ 5 cc[1*]
Sacral plexus	Dmax ≤ 26 Gy[12] (+ nerve roots)	Dmax ≤ 24 Gy[1] V22.5 Gy ≤ 5 cc[1]	D_{max} ≤ 29 Gy [1*] V27 Gy ≤ 5 cc[1*]	Dmax ≤ 32 Gy[1] V30 Gy ≤ 5 cc[1]	Dmax ≤ 39 Gy[1*] V36 Gy ≤ 5 cc[1*]
Brainstem	NA	(not medulla) Dmax ≤ 23.1 Gy[1] V18 Gy ≤ 0.5 cc[1]	(not medulla) Dmax ≤ 28 Gy[1*] V21 Gy ≤ 0.5 cc[1*]	(not medulla) Dmax ≤ 31 Gy [1] V23 Gy ≤ 0.5 cc[1]	NA
Optic Pathway	Dmax≤ 15.8 Gy[17] D0.2cc≤ 11.5Gy [17]	Dmax ≤ 19.5 Gy[17] D0.2cc ≤ 15.0 Gy[17]	Dmax ≤ 22.5 Gy[17] D0.2cc ≤ 17.5Gy[17]	Dmax ≤ 25 Gy[17] D0.2cc ≤ 20 Gy[17]	NA NA
Cochlea	Dmax ≤ 16.5 Gy[18]	Dmax ≤ 20 Gy[18]	Dmax ≤ 22.5 Gy[18]	Dmax ≤ 25.0 Gy[18]	NA
Parotids (each)	Mean ≤ 7 Gy[12]	NA	NA	NA	NA
Pharynx	Dmax ≤ 20Gy[12] Mean ≤ 9Gy[12]	NA	NA	NA	NA
Larynx	Dmax ≤ 20Gy[12] Mean ≤ 9Gy[12]	NA	NA	NA	NA
PBT and PT (prox. bronch tree & prox. trachea)	Dmax ≤ 20 Gy[12]	Dmax ≤ 30 Gy [1]	Dmax ≤ 34.8 Gy[3]	Dmax ≤ 40 Gy[1]	Dmax ≤ 46.3 Gy[3*]
Lungs-GTV	NA	>1500cc ≤ 11.6 Gy[1] V18 Gy ≤ 10%[3,8*] Mean ≤ 5.5 Gy [8*]	1500cc≤ 11.6 Gy[3] V20 Gy ≤ 10%[3,8] Mean ≤ 6 Gy [8]	>1500cc ≤12.5 Gy[1] V22 Gy ≤ 10%[3,8*] Mean ≤ 6.5 Gy [8*]	> 1500c ≤ 14 Gy[3*] V26Gy ≤ 10%[3,8*] Mean ≤ 7 Gy [8*]

OAR	SABR ORGAN-AT-RISK (OAR) CONSTRAINTS Dmax to ≤=0.035cc for all OARs. Exception: Dmax to 0cc (hard max) → Spinal cord, Spinal cord PRV, Thecal sac/Cauda Equina				
	Fractions				
	2 (for spine mets only as per CCTG SC24)	**3**	**4**	**5**	**8**
Each Lung	V5 Gy ≤ 35%[12] V10 Gy ≤ 10%[12] V20 Gy ≤ 3%[12] Mean ≤ 5 Gy[12]	NA	NA	NA	NA
Chest wall and Ribs:	Dmax ≤ 36.5 Gy[7*] V25Gy < 30cc[6*]	Dmax ≤ 44 Gy[7] V30 Gy ≤ 30 cc[6]	Dmax ≤ 50 Gy[7] V34 Gy ≤ 30 cc[6]	Dmax ≤ 55Gy[7] V37 Gy ≤ 30cc[6]	Dmax ≤ 68 Gy[7] V45 Gy ≤ 30 cc[6]
Brachial Plexus	NA	Dmax ≤ 24 Gy[1] V20.4 Gy ≤ 3cc[1]	Dmax ≤ 26 Gy[4] V23.6 Gy ≤ 3 cc[3]	Dmax ≤ 30.5 Gy[1] V27 Gy ≤ 3 cc[1]	Dmax ≤ 35 Gy[4]
Heart / Pericardium	NA	Dmax ≤ 30 Gy[1] V24 Gy ≤ 15 cc[1]	Dmax ≤ 34 Gy[3] V28 Gy ≤ 15 cc[3]	Dmax ≤ 38 Gy[1] V32 Gy ≤ 15 cc[1]	Dmax ≤ 46 Gy[2] V39 Gy ≤ 15 cc[2]
Great Vessels	Dmax ≤ 40 Gy[20]	Dmax ≤ 44 Gy[20]	Dmax ≤ 49.0 Gy[20]	Dmax ≤ 51.5 Gy[20]	Dmax ≤ 65 Gy[2]
Skin	Dmax < 26 Gy[1*] V24 Gy < 10 cc[1*]	Dmax ≤ 33 Gy[1] V30Gy ≤ 10 cc[1]	Dmax ≤ 36 Gy[3] V33.2 Gy ≤ 10 cc[3]	Dmax ≤ 39.5 Gy[1] V36.5 Gy ≤ 10 cc[1]	Dmax ≤ 48 Gy[3*] V44 Gy ≤ 10 cc[3*]
Esophagus	Dmax ≤ 20 Gy[12]	Dmax ≤ 27.0 Gy[21]	Dmax ≤ 30 Gy[3, 21]	Dmax ≤ 35 Gy[1, 21]	Dmax ≤ 40 Gy[2]
Stomach	Dmax ≤ 20 Gy[12]	Dmax ≤ 22.2 Gy[1] (Dmax ≤25 Gy if PTV close by; MRP to specify[14])	Dmax ≤ 27[3]	Dmax ≤ 32 Gy[1] (Dmax ≤ 35 Gy if PTV close by ; MRP to specify[14])	Dmax ≤ 40 Gy[2]
Duodenum	Dmax ≤ 20 Gy[12]	Dmax ≤ 22.2 Gy[1] (Dmax ≤25 Gy if PTV close by ; MRP to specify[14])	Dmax ≤ 29.0 Gy[1*]	Dmax ≤ 32 Gy[1,22] Dmax ≤ 35 Gy if PTV close by ; MRP to specify[14])	Dmax ≤ 39 Gy[2]
Small Bowel (Jejunum/ileum)	Dmax ≤ 20 Gy[12]	Dmax ≤ 25.2 Gy[1, 23]	Dmax ≤ 28.5 Gy[23]	Dmax ≤ 29.0 Gy[23] (Dmax ≤ 35 Gy[1] if PTV close by MRP to specify)	Dmax ≤ 40 Gy[2]
Large Bowel (Colon, Rectum)	Dmax ≤ 20 Gy[12]	Dmax ≤ 28.2 Gy[1]	D_{max} ≤ 34.5 Gy[1*]	Dmax ≤ 38 Gy[1]	Dmax ≤ 46 Gy[1]
Kidneys (each)	Dmax ≤ 26 Gy[12] Mean ≤ 6 Gy[12] (*each kidney)	NA	NA	NA	NA
enal Cortex (Kidneys) (R & L combined)	See "Kidneys (each)"	> 200 cc ≤ 14.4 Gy[2]	> 200 cc < 16.2Gy[1*]	> 200cc ≤ 17.5 Gy[1]	> 200 cc ≤ 21 Gy[2]
Liver (Liver minus GTV)	Dmax ≤ 26 Gy[12] Mean ≤ 8 - 9 Gy[12]	>700 cc ≤ 17 Gy[1]	>700 cc ≤ 19 Gy[1*]	> 700 cc ≤ 21Gy[1]	> 700 cc ≤ 22 Gy[2]
Bladder Wall	NA	Dmax ≤ 28.2 Gy[1]	D_{max} ≤ 34.5 Gy[1*]	Dmax ≤ 38 Gy[1]	NA

Penile Bulb	NA	Dmax ≤ 42 Gy [1] V21.9 Gy ≤ 3 cc[1]	NA	Dmax ≤ 50 Gy[1] V30 Gy ≤ 3 cc[1]	NA
Femoral Heads (R & L combined)	NA	V21.9 Gy ≤ 10 cc[1]	V27 Gy ≤ 10 cc [1*]	V30 Gy ≤ 10 cc[1]	NA

*Values are EQD2 conversion from stated reference

Table 6. Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional Radiotherapy (nBED)	1 fraction: SBRT dose to thecal sac P_{max}	2 fractions: SBRT dose to thecal sac P_{max}	3 fractions: SBRT dose to thecal sac P_{max}	4 fractions: SBRT dose to thecal sac P_{max}	5 fractions: SBRT dose to thecal sac P_{max}
0*	10 Gy	14.5 Gy	17.5 Gy	20 Gy	22 Gy
20 Gy in 5 fractions ($30\ Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
30 Gy in 10 fractions ($37.5\ Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
37.5 Gy in 15 fractions ($42\ Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
40 Gy in 20 fractions ($40\ Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
45 Gy in 25 fractions ($43\ Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fractions ($50\ Gy_{2/2}$)	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy

Abbreviations: N/A = not applicable; nBED = normalized biologically effective doses; SBRT = stereotactic body radiotherapy.
* These dose limits are based on our prior publication for spinal cord tolerance in patients treated with SBRT and no prior history of radiation (7).

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PROTOCOL SIGNATURE PAGE

Protocol Title: Phase II non-randomized Trial of Stereotactic Ablative Radiotherapy (SABR) for Oligometastases

Protocol Version/ Date: _____

Sponsor/Study Principal Investigator Name: Dr. Robert Olson

Site: _____

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments, and I agree to:

- conduct the described trial in compliance with all stipulations of the protocol, with applicable regulatory requirement(s), and ICH E6 Guideline for Good Clinical Practice (GCP);
- comply with procedures for data entry/recording/reporting as outlined in the data management plan;
- permit monitoring, auditing and inspection; and
- retain the trial related essential documents until Dr. Robert Olson (Study Principal Investigator) informs me that these documents are no longer needed.

Site Principal Investigator Name: _____

Site Principal Investigator Signature: _____

Date: _____