Protocol Title: Phase III Randomized Controlled Trial and Economic Evaluation of Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic (1-3 metastases) cancer: **SABR-COMET-3**

Protocol Number:

Version Number and Date: 13.0; 15 May 2024

Study Phase: III

Short Title: SABR-COMET-3

Sponsor Name: BC Cancer – Prince George

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Version 12.0; 01 May 2023

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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.

See electronic signature

Dr. Robert Olson **Date**

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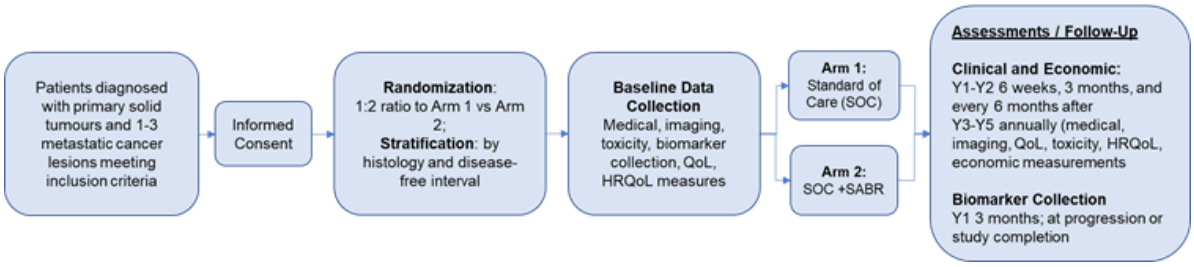
II. LIST OF ABBREVIATIONS

Abbreviations	Description of Abbreviations
AE	Adverse event
BPI	Brief Pain Inventory
CRF	Case report form
CI	Confidence Interval
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
EORTC	European Organisation for Research and Treatment of Cancer.
EQ-5D-5L	EuroQol-5 Dimension-5 Level
FACT	Functional Assessment of Cancer Therapy
GCP	Good Clinical Practice
GTV	Gross Tumour Volume
Gy	Gray
HCP	Health Care Provider
HRQoL	Health-Related Quality of Life
ICF	Informed consent form
ICH	International Council for Harmonization
OAR	Organs at Risk
OS	Overall Survival
PD	Progressive Disease
PFS	Progression free survival
PRO	Patient Reported Outcomes

PTV	Planning Target Volume
QALYS	Quality-Adjusted Life Year
QoL	Quality of Life
REB	Research Ethics Board
RECIST	Response evaluation criteria in solid tumors
RT	Radiation therapy
SABR	Stereotactic Ablative Radiotherapy
SAE	Serious adverse event
SOP	Standard Operating Procedure
SPI	Study Principal Investigator

1. Protocol Summary

1.1. Synopsis

Date and Version # of Protocol:	15 May 2024, Version 13.0
Sponsor: BC Cancer	
Name of Study Method: Randomized Controlled Trial	**Phase of Development:** III
Title of Study: Phase III Randomized Controlled Trial and Economic Evaluation of Stereotactic Ablative Radiotherapy (SABR) for Comprehensive Treatment of Oligometastatic (1-3 metastases) cancer: SABR-COMET-3	
Study Design Overview/Rationale: This is a study assessing the impact of SABR, compared to standard of care treatment, on overall survival, oncologic outcomes, and quality of life in *patients with 1-3 metastatic lesions. *Note: the terms patients and subjects are used interchangeably in this protocol	
Trial Design and Schema  	

Radiation Treatment Plan Arm 1: Standard of Care (SOC)

Table 1. Dose and Fractionation - SOC

Dose (Gy)	Fractions	Dose/Fractionation
8 Gy	1	8Gy
20 Gy	5	4Gy
30 Gy	10	3Gy

Radiation Treatment Plan (Arm 2):

Table 2 Dose and fractionations by site with [secondary options in square brackets]

Location		Dose (Gy)	Fractions	Dose per fraction (Gy)	Frequency
Lung Tumors 5 cm or less surrounded by lung parenchyma		48 Gy [54 Gy]	4 [3]	12 Gy [18 Gy]	Daily, or Every second day
Within 2 cm of mediastinum or brachial plexus		60 Gy	8	7.5 Gy	Daily
Bone Any bone		35 Gy [24]	5 [2]	7 Gy [12 Gy]	Daily
Brain Stereotactic lesions (no whole brain Radiation Therapy [RT])	< 2cm	20-24 Gy	1	20-24 Gy	Once
	2-3 cm	18 Gy	1	18 Gy	Once
Metastases only		35 Gy	5	7 Gy to PTV	Daily
Whole brain + Metastases		35 Gy to metastases 20 Gy whole brain	5	7 Gy to PTV 4 Gy WBRT	Daily
Liver		54 Gy	3	18 Gy	Every second day
Adrenal / Pancreas		40 Gy [35 Gy]	5	8 Gy [7 Gy]	Daily
Lymph Node/Soft Tissue		40 Gy	5	8 Gy	Daily
**Either bone or positron emission tomography (PET) scan is required. If PET is done, bone scan is not required (or vice versa)*					

Disease Assessment:

- Eastern Cooperative Oncology Group (ECOG) performance status
- Overall Survival
- Progression Free Survival
- Patient Reported Outcomes (i.e. Quality of life assessment, questionnaires, etc.)
- Provider Reported Toxicity (as per Common Terminology Criteria for Adverse Events (CTCAE) v5.0)
- Health Related Quality of Life
- Correlation between candidate biomarkers and oncologic outcomes

Study Population

Patients diagnosed with 1 controlled primary tumour and 1-3 current metastatic lesions, and maximum of 8 lifetime metastatic lesions, as evidenced by imaging, meeting all eligibility criteria

Study Objectives:

Primary Objective

To compare the effect of SABR and Standard of Care (SOC), relative to SOC alone, on overall survival (OS) in patients with controlled primary solid tumors and 1-3 current metastatic cancer lesions.

Secondary Objectives:

Secondary Objectives:

- To compare side effects, in terms of the occurrence of grade 2 or higher adverse events
- To compare changes in progress-free survival (PFS)
- To compare changes in patient-reported quality of life (QoL)
- To estimate the cost-effectiveness of SABR versus SOC
- To assess the correlation between candidate biomarkers of oligometastatic disease (blood- derived) and oncologic outcomes, including response to SABR, disease progression, and overall survival

Number of Subjects/Sample Size Calculations

330 subjects will be accrued

The results of the original SABR-COMET phase II trial demonstrated median OS of 28 months in the standard arm, 41 months in the experimental arm, and a 22% improvement in 5-year OS. Based on these results, this phase III trial initially aimed to detect a Hazard Ratio of death of 0.66 in the experimental arm compared to the standard arm (i.e. a 40% reduction in the hazard rate of death). A 5-year OS of 20% had been assumed for the standard arm; the HR of 0.66 represents a 15% improvement in OS, smaller than the effect observed in the phase II trial. In order to detect this difference, with 80% power, alpha of 0.05, and an 8% dropout rate, assuming 5 years of accrual and a total trial time of 8 years, 297 patients would be required (i.e. 99 in Arm 1 and 198 in Arm 2).

Amendment June 2022:

Study sample size was increased to 330 (110 in Arm 1 and 220 in Arm 2). This sample size will provide 80% power to detect an improvement in median OS from 16 months to 27 months allowing for 5% dropout. This assumes 5 years of accrual and 1 year of additional follow-up.

Planned Study Period:

Anticipated length of study is 11 years

Inclusion Criteria:

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

- Total number of 1-3 current metastases, and a maximum 8 lifetime metastases
- Age 18 or older
- Able to provide informed consent
- Life expectancy >6 months

- Histologically confirmed malignancy with metastatic disease detected on imaging. Biopsy of metastasis is preferred, but not required.
- ECOG performance status 0 – 2
- Controlled primary tumor
  - defined as at least 3 months since original tumor treated definitively, with no progression at primary site (can be considered controlled if no evidence of the primary tumour on imaging)
- A history and physical exam, including ECOG performance status, performed **within 6 weeks prior to trial enrollment**
- Not suitable for resection at all sites or declined surgery
- Subject has had a CT chest, abdomen and pelvis or PET-CT within 8 weeks prior to enrollment, and with 12 weeks of treatment. CT neck as clinically indicated.
- Patient has had a nuclear bone scan (if no PET-CT) within 8 weeks prior to enrollment, and within 12 weeks prior to treatment (if randomized to SABR)
- If solitary lung nodule for which biopsy is unsuccessful or not possible, patient has had an FDG (fluorodeoxyglucose) PET scan or CT (chest, abdomen, pelvis) and bone scan within 8 weeks prior to enrollment, and with 12 weeks prior to treatment (if randomized to SABR). CT neck as clinically indicated.
- If colorectal primary with rising Carcinoembryonic antigen (CEA), but equivocal imaging, patient has had an FDG PET scan within 8 weeks prior to enrollment, and with 12 weeks prior to treatment (if randomized to SABR)
- Patient has had CT or MRI brain imaging if primary has a propensity for CNS metastasis within 8 weeks prior to enrollment, and with 12 weeks prior to treatment (if randomized to SABR)
- Patient is judged able to:
  - Maintain a stable position during therapy
  - Tolerate immobilization device(s) that may be required to deliver SABR safely
- Negative pregnancy test for Women of Child-Bearing Potential (WOCBP) **within 4 weeks of RT start date**
- Patient is able and willing to complete the quality of life questionnaires, 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)

Waivers to inclusion criteria will NOT be allowed.

Exclusion Criteria:

- Lesion in femoral bone requiring surgical fixation
- Chemotherapy agents (cytotoxic, or molecularly targeted agents) used within the period of time commencing 2 weeks prior to radiation, lasting until 1 week after the last fraction for patients randomized to SABR.
- Serious medical comorbidities precluding radiotherapy. These include interstitial lung disease in patients requiring thoracic radiation, Crohn's disease in patients where the GI tract will receive radiotherapy, and connective tissue disorders such as lupus or scleroderma.

- Substantial overlap with a previously treated radiation volume. Prior radiotherapy in general is allowed, as long as the composite plan meets dose constraints herein. For patients treated with radiation previously, biological effective dose calculations should be used to equate previous doses to the tolerance doses listed below. All such cases should be discussed with the local and study PIs.
- Concurrent malignant cancer, or history of malignant cancers within the past 5 years
- Malignant pleural effusion
- History of poor lung function (if treating near lung)
- History of poor liver function (if treating near liver)
- Inability to treat all sites of disease
- Maximum size of 5 cm for lesions outside the brain, except:
    - Bone metastases over 5 cm may be included, if in the opinion of the local PI it can be treated safely (e.g. rib, scapula, pelvis)
    - Any brain metastasis >3 cm in size or a total volume of brain metastases greater than 30 cc
- Clinical or radiologic evidence of spinal cord compression, or epidural tumor within <2 mm of the spinal cord. Patients can be eligible if surgical resection has been performed, but the surgical site counts toward the total of up to 8 lifetime metastases (see section 3.2).
- Dominant brain metastasis requiring surgical decompression
- Pregnant or breastfeeding women

Waivers to exclusion criteria will NOT be allowed.

Concomitant Medication Restrictions or Requirements:

Required / Permitted:

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

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

Restrictions (for patients randomized to SABR):

- 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, adriamycin/doxorubicin, bevacizumab) are **discouraged within the first month after radiation**.

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[15]. **Grade 2 or higher toxicities that are possibly, probably, or definitely related to any cancer treatment must be documented and reported as AEs/SAEs for both arms**.

All Grade 3 or higher toxicities, related or not to cancer treatment, must also be documented, though start and stop dates do not need to be collected for toxicities considered to be unrelated or unlikely related to cancer treatment

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 as per REB and institutional reporting guidelines.

Conditions that are NOT considered a SAE will not be included in this protocol, e.g., hospitalizations for routine procedures, disease progression, death due to disease progression.

Formal Stopping Rules:

Accruing 330 subjects will increase confidence in the safety of SABR treatment (i.e. less grade 4 or 5 toxicity, etc.).

There will be 3 interim analyses. The data and safety monitoring committee (DSMC) will conduct the first interim analysis once 50 patients are accrued. For this analysis, the DSMC will be blinded to the identity of each treatment arm, but OS data will be presented for each arm, and treatment doses and volumes will be presented for SAEs reviewed. There are two planned interim analyses for efficacy in addition to the final analysis. The two interim analyses are expected to be carried out when the total number of observed study deaths reaches 40 and 65, thus treatment details will be reviewed to determine plausible causation of toxicities. As such, interim efficacy analyses will not be blinded. The DSMC will recommend stopping the trial if there is an OS difference that is statistically significant with a threshold of $p<0.001$ using the log-rank test. The final analysis is expected to be carried out 3 years after the enrollment of the last subject.

Statistical Evaluations:

Patients will be analyzed in the groups to which they are assigned (intention-to-treat).

Survival Endpoints

Progression-Free Survival (PFS) and Overall Survival (OS) will be calculated using the Kaplan-Meier method with differences compared using the stratified log-rank test. Pre-planned subgroup analysis will occur based on the stratification factors, and also based on the use of immunotherapy vs. non-immunotherapy systemic agents. 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. **Secondary Endpoints** Quality of life at 6 months will be measured using FACT, Cancer Specific Questionnaires, and EQ-5D-5L scores, with differences between groups tested using the Student's t-test. Differences in rates of grade 2 or higher toxicity between groups will be tested using the Fisher's Exact Test. EQ-5D-5L scores will be converted to quality -adjusted life years (QALYS) and combined with resource utilization data for the cost utility analysis (restricted to Canada).
Endpoints for Evaluation: Overall Survival Progression-Free Survival Toxicity Quality of Life Health-Related Quality of Life Resource Utilization Correlation between candidate biomarkers of oligometastatic disease (blood-derived) and oncologic outcomes

2. Introduction

2.1. Trial Rationale and Background

The **oligometastatic state** refers to a stage of disease where a cancer has spread beyond the site of the primary tumour, but is not yet widely metastatic.[1] In patients with a limited oligometastatic burden, emerging evidence suggests that treatment of all sites of disease with ablative therapies (such as surgery or stereotactic radiation) can improve patient outcomes, including overall- and progression-free survival.

Historically, evidence to support the oligometastatic state has consisted of single-arm, non-randomized studies without controls[2,3]. One classic study reported on over 5000 patients with lung metastases from a variety of primary tumours. In patients who achieved a complete resection of their lung metastases, 5-year overall survival (OS) was 36%, better than might be expected for a cohort of patients with metastatic disease.[2] Similarly, after radiation, a recent pooled analysis of 361 patients with oligometastatic lesions treated with radiation demonstrated a 3-year OS of 56%.[3]

It has been suggested the long-term survivals achieved in patients with oligometastases after ablative therapies is merely due to the selection of very fit patients with slow growing tumours, since randomized evidence to support the oligometastatic paradigm has been lacking.[4,5] However, at least four recent randomized phase II trials now provide some supporting, though non-conclusive, evidence.

Randomized Evidence Supporting the Oligometastatic State

Two of these trials supporting the use of oligometastatic treatment were done in the setting of oligometastatic non-small cell lung cancer. In both, patients presented with a primary lung tumour and a limited number of metastatic lesions (1-3 in one trial, 1-5 in the other), and after initial systemic therapy, patients were randomly assigned to standard palliative treatments vs. consolidative ablative treatments to all sites of disease. Both trials were stopped early due to evidence of efficacy, with the ablative treatments achieving a ~3-fold improvement in progression-free survival (PFS)[5,6]. No OS data was reported in these trials but based on their results, the phase III NRG LU-002 trial is assessing the impact of consolidative ablative therapies on OS.

A third trial, EORTC 40004, examined the impact of an ablative therapy (radiofrequency ablation [RFA]) in patients with colorectal cancer metastatic to the liver. In this trial, patients with a controlled primary tumour and fewer than 10 hepatic metastases not amenable to resection, and with no extra-hepatic disease, were randomized to systemic therapy +/- RFA to all sites of disease[67,]. When initially reported, the trial showed no difference in OS between arms, but with long-term follow-up (median 9.7 years), a significant difference in OS emerged, with an 8-year OS of 36% in the RFA arm and only 9% in the systemic therapy arm[7,8].

The fourth trial, Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Disease (SABR-COMET) enrolled 99 patients who had controlled primary solid tumours and up to 5 metastatic lesions[7]. Patients were randomized in a 1:2 ratio between standard of care (SOC) palliative treatments (Arm 1) vs. SOC + SABR to all sites of disease (Arm 2).[9] The primary endpoint was OS, and the trial employed a randomized phase II screening design, with an alpha of 0.2, in order to provide an initial comparison between arms. More than 90% of patients enrolled had 1-3 metastases[7]. OS was 28 months in Arm 1 and 41 months in Arm 2 (p=0.09), meeting the primary endpoint of the trial. PFS was doubled: 6 months in Arm 1 and 12 months in Arm 2 (p=0.001). SABR was generally well tolerated, with a 29% rate of grade 2 or higher toxicity, although the rate of treatment-related grade 5 toxicity was 4.5%[9].

The results of SABR-COMET met the pre-specified primary endpoint, with a trend toward improved OS with SABR, and have informed the design of this phase III randomized trial. This phase III trial will focus specifically on patients with 1-3 metastases, which comprised 92% of the patients on the SABR-COMET trial, as there was reluctance to accrue patients with 4-5 metastases, and theoretically survival benefit is hypothesized to be greatest in those with 1-3 metastases. This phase III trial incorporates stratification by histology and disease-free interval, as well as both economic and translational aims.

Translational Studies: Background & Rationale

At the present time, there are no biomarkers that define the oligometastatic state. The closest to a defining biological feature is tumour histology, of which breast, kidney, and prostate are associated with improved OS in patients with clinical oligometastatic disease[10]. Key clinical characteristics - colloquially termed 'The Four Aces'[10] - help to identify a patient sub-population with metastatic cancer that is most likely to benefit from ablation of all sites of disease.

Even within this group, however, outcomes can be variable: while some patients exhibit long disease-free intervals and better-than-expected overall survival following ablation of metastases, others progress rapidly and extensively with poor survival outcomes[12]. Elucidating the biological mediators underlying a more indolent, sequential pattern of progression (i.e., oligometastasis) versus rapid, "poly-metastatic" progression will allow for more accurate selection of patients whose intrinsic natural history of disease make them more likely to benefit from ablation.

Specific biological characteristics of oligometastatic disease could provide important predictive biomarkers in this setting, but have thus far remained elusive. Studies up to this point have focused on micro-RNA (ribonucleic acid) profiling, but unfortunately these studies have not identified an miRNA (microRNA) expression signature that consistently defines patients with few metastases[13-15]. No other studies to our knowledge have sought to identify specific biomarkers of oligometastasis. While a wide array of pre-clinical analyses have identified genetic and epigenetic alterations associated with metastasis in general,[16] it remains to be determined which of these features represent useful biomarkers in differentiating rapid and widely metastatic cancer from an

oligometastatic natural history. **As such, the purpose of the translational arm of this trial is to assess the correlation between candidate biomarkers of oligometastatic disease (blood-derived) and oncologic outcomes including response to SABR, disease progression, and overall survival.**

2.2. Radiation Treatment Overview

2.2.1. Radiation therapy – Standard of Care (SOC) Arm (Arm 1)

Arm 1 (SOC): Radiotherapy (RT) for patients in the standard arm will follow the principles of palliative RT, with the goal of alleviating symptoms or preventing imminent complications. RT given should be to palliate symptoms rather than ablate tumours (exceptions exist such as brain metastases). Chemotherapy, hormonal agents, and targeted anti-cancer systemic therapy may be used at the discretion of the patients' treating oncologist and will not be mandated by the trial, but will be prospectively collected to inform the cost-effectiveness analysis. If palliative RT is indicated, treatment planning is to be done using computed tomography (CT) simulation or conventional simulation (fluoroscopy) as per individual institutional practice. Simple beam arrangements (e.g. parallel opposed beams), are favored wherever possible, and doses should be limited to 8 Gy in 1 fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions, though on subsequent progression, SABR may be used per institutional policy, though not encouraged.

2.2.2. Radiation therapy - Experimental Arm – SABR + SOC (Arm 2)

For Arm 2 (SABR), all treatments in this study are based on our phase II SABRCOMET trial, further refined per recent evidence of normal tissue tolerance, the toxicities observed in that trial, and emerging relative contraindications to SABR[1]. The guiding principle for RT is to achieve disease control and minimize any potential adverse impact on quality of life (QoL). 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**. Hormone therapy is permitted. Prior surgery to a metastatic site is permitted, but it will be counted towards the total of 8 lifetime metastases. Doses and fractionations by tumour site are shown in **Table 2 (Section 5.1.2)**. Treatment will be setup using reproducible positioning, verified using an on-line protocol, for all patients in this study.

All patients in Arm 2 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[17,18]. 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 3 (Appendix)**. Planning detail parameters will be similar to the phase II trial, and will be well outlined for planners.

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 pain, 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 pain, 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 abdominal pain, 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

2.2.3. Sample Collection Schedule (participating sites only)

The translational component of this trial is not mandatory, however has been designed to minimize the impact on patients while addressing important research questions around the oligometastatic state. Specifically, the increased requirements, beyond standard of care testing, consist of drawing 3 tubes of blood at 3 time periods (Figure 1): at randomization (baseline), 3-months post-treatment, and at progression. In patients who do not progress, the final sample will be drawn at study completion (5-years post randomization).

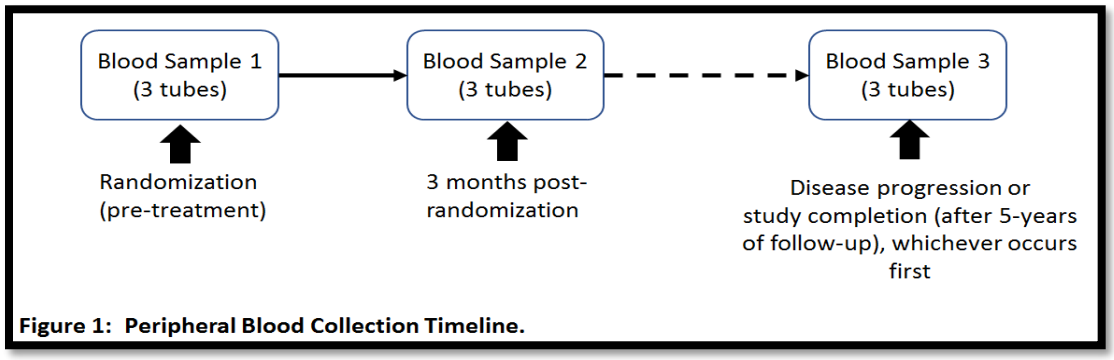


Figure 1: Peripheral Blood Collection Timeline.

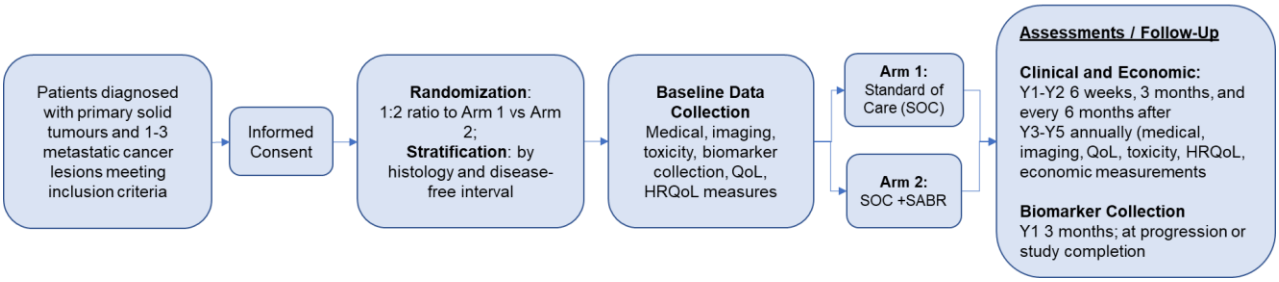
2.3. Study Population

Patients with 1 controlled primary solid tumour and 1-3 current metastatic cancer lesions, and maximum 8 lifetime metastatic lesions (e.g. could have had 5 brain lesions treated with fractionated stereotactic radiotherapy previously, but 3 current lesions), as evidenced by imaging, meeting all eligibility criteria.

3. Trial Design

This study is a phase III multicentre randomized trial. Patients will be randomized in a 1:2 ratio between current standard of care treatment (Arm 1) vs. standard of care treatment + SABR (Arm 2) to sites of known disease.

Patients will be stratified by two of the strongest prognostic factors, based on a large multi-institutional analysis[18]: histology (Group 1: prostate, breast, or renal; Group 2: all others), and disease-free interval (defined as time from diagnosis of primary tumour until first detection of the metastases being treated on this trial; divided as ≤2 years vs >2 years).



3.1. Study Objectives and Endpoints

3.1.1 Objectives

Primary Objective

To compare the effect of SABR and SOC, relative to SOC alone, on overall survival in patients with controlled primary solid tumours and 1-3 current metastatic cancer lesions

Secondary Objective(s)

- To compare side effects, in terms of the occurrence of grade 2 or higher adverse events
- To compare changes in progress-free survival (PFS)
- To compare changes in patient-reported quality of life (QoL)
- To estimate the cost-effectiveness of SABR versus SOC
- To assess the correlation between candidate biomarkers of oligometastatic disease (blood-derived) and oncologic outcomes, including response to SABR, disease progression, and overall survival

3.1.2 Endpoints

Primary Endpoint:

- Overall Survival

Secondary Endpoint(s):

- Progression-Free Survival
- Toxicity
- Quality of Life
- Health-Related Quality of Life
- Resource Utilization
- Correlation between candidate biomarkers of oligometastatic disease (blood-derived) and oncologic outcomes

3.2. Entry Procedures

- **History and Physical Examination <u>within 6 weeks of study accrual (No exceptions to timelines):</u>**
  - Including prior cancer therapies and cancer-specific concomitant medications (for example, systemic therapy such as immunotherapy, hormone therapy and/or chemotherapy drugs and regular/supporting medications such as anti-emetics).

- **Restaging <u>within 8 weeks prior to randomization, and with 12 weeks of treatment for patients randomized to SABR (No exceptions to timelines):</u>**
  - **Brain**: CT or MRI for tumour sites with propensity for brain metastasis. All patients with brain metastases at enrollment or previously require an MRI.
  - **Body**: 18-FDG PET/CT imaging is strongly recommended, except for tumours where FDG update is not expected (e.g. prostate, renal cell carcinoma). PSMA-PET or choline-PET is recommended for prostate cancer. In situations where a PET scan is unavailable, or for tumours that do not take up radiotracer, CT chest/abdomen/pelvis with bone scan is required. CT Neck as clinically indicated.
  - **Spine**: MRI required for patients with vertebral or paraspinal metastases, though the MRI can be limited to the involved segment, including at least the involved vertebral body(ies) plus 2 vertebral bodies above and below, where applicable.

- Pregnancy test for women of child-bearing potential **<u>within 4 weeks of RT start date (No exceptions to timeline)</u>**
- Complete Blood Count (CBC) **within 8 weeks prior to randomization**

- Pulmonary function tests, if previously documented poor lung function, treating near lung, and at discretion of investigator
- Liver function tests, if poor liver function, treating near liver, and at discretion of investigator

Defining number of metastases:

Patients are eligible if there are a maximum of 1-3 current metastatic lesions present. Each discrete lesion is counted separately. For patients with lymph node metastases, each node is counted as one site of metastasis. All known metastatic lesions must be targetable on planning CT. For patients where the lesion is only detectable on MRI, fusion of the MRI with the planning CT is required.

Patients with prior metastases that have been treated with ablative/RT therapies (e.g. SABR, surgery, radiofrequency ablation) are eligible, as long as those metastases are controlled on imaging, and the total number of previously treated and current metastases does not exceed 8. (Brain metastases have to have been treated, or will be treated, with ablative technique (surgery SRS, or SRT)). In addition, if the previous lesions are treated with SABR, SRT, or SRS, there must be repeat imaging >/= 3 months after treatment showing disease stability or shrinkage.

When patients have small indeterminate nodules (e.g. a 2 mm lung nodule) it can be difficult to determine whether these are benign or whether they represent metastasis. Any such lesion that is 'new' is automatically considered a metastasis unless there are >2 months of documented stability without systemic therapy.

Brain Metastases at Presentation

If a patient presents with 1-2 brain metastases and ablation of those metastases (with surgery or radiation) is judged to be clinically required regardless of the treatment of extracranial metastases, ablative treatment is permitted. Those treated metastases count within the total number of 3 lesions. The patient would then be randomized to treatment of the extracranial disease. For example, a patient with a solitary brain metastasis and two lung metastases could receive an ablative technique to the brain (e.g. surgery, stereotactic radiosurgery [SRS], or fractionated stereotactic radiotherapy [FSRT]), and then be randomized to SABR vs SOC for the two lung metastases.

Patients Already Receiving Systemic Therapy

If a patient is already receiving systemic therapy, they are still eligible for enrolment. For example, if a patient with 2 metastases has been on systemic therapy for a year and is planning to continue, they can still be randomized, and if allocated to the standard arm would continue to receive systemic therapy, though on the experimental arm will receive SABR between cycles, and may require a short treatment break.

a) Randomization

The study will employ a 1:2 randomization between Arm 1:Arm 2, with further stratification between 1) histology (Group 1: prostate, breast, or renal; Group 2: all others), and 2) disease-free interval (defined as time from diagnosis of primary tumour until first detection of the metastases being treated on this trial; divided as ≤2 years vs >2 years).

Permuted block randomization will be used to reduce selection bias, promote allocation concealment, and improve balance across groups over the trial period. Patients will be randomized based on a permuted block design using a block size based on a multiple of 3 (with block size known only to statistician until analysis is completed, per ICH E9)[20]. The Coordinating Centre and trial statistician will be responsible for configuring the module within the electronic data capture (EDC) system that will be used to randomize participants.

b) Blinded/Unblinded

This is an open-label randomized controlled study design; however, during interim and final analyses, outcomes assessors and data analysts will be blinded to the identity of each treatment arm, however treatment doses and volumes will be presented for SAEs reviewed.

3.3. Study Duration

Study duration is expected to be 11 years, per activities listed below:

Trial Activities	Start date	Expected End date
Database setup, CRF Development	31-Dec-18	30-Sep-19
Ethics/Site Approval and Clinical Trial Registration	31-Dec-18	27-Feb-19
Site Training / Initiations	1-May-19	31-Oct-20
Patient Recruitment	1-Nov-19	30-Jun-25
Patient Follow-up	1-Dec-19	30-Jun-30
Interim Data Analysis (est)	1-Jul-21	1-Jul-22
Interim Data Analysis (est)	1-Jul-22	31-Dec-24
Interim Data Analysis (est)	1-Jan-24	30-Jun-25
Database Lock / Final Analyses / Knowledge Translation	1-Aug-29	31-Dec-30

4. Eligibility

Waivers to eligibility criteria are not permitted.

See Eligibility Checklist (Subject Registration Form)

4.1. Inclusion Criteria

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

- Total number of 1-3 current metastases, and a maximum of 8 lifetime metastases
- Age 18 or older
- Able to provide informed consent
- ECOG performance status 0 – 2
- Life expectancy >6 months
- Histologically confirmed malignancy with metastatic disease detected on imaging. Biopsy of metastasis is preferred, but not required.
- Controlled primary tumour
    - defined as: at least 3 months since original tumour treated definitively, with no progression at primary site (can be considered controlled if no evidence of primary tumour on imaging)
- A history and physical exam including performance status performed within 6 weeks prior to trial enrollment
- Not suitable for resection at all sites or declined surgery
- Patient has had a CT chest, abdomen and pelvis or PET-CT within 8 weeks prior to enrollment, and within 12 weeks prior to treatment if randomized to SABR. CT Neck as clinically indicated.
- Patient has had a nuclear bone scan (if no PET-CT) within 8 weeks prior to enrollment, and within 12 weeks prior to treatment if randomized to SABR,
- 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 within 8 weeks prior to enrollment, and within 12 weeks prior to treatment if randomized to SABR. CT Neck as clinically indicated.
- If colorectal primary with rising CEA, but equivocal imaging, patient has had an FDG PET scan within 8 weeks prior to enrollment, and within 12 weeks prior to treatment if randomized to SABR,
- Patient has had CT or MRI brain imaging if primary has a propensity for CNS metastasis within 8 weeks prior to enrollment, and within 12 weeks prior to treatment if randomized to SABR,
- Patient is judged able to:
    - Maintain a stable position during therapy
    - Tolerate immobilization device(s) that may be required to deliver SABR safely

- Negative pregnancy test for Women of Child-Bearing Potential (WOCBP) ***within 4 weeks of RT start date***
- Patient is able and willing to complete the quality of life questionnaires, and other assessments that are a part of this study, via paper or online using REDCap (if email is provided by participant on informed consent)

4.2. Exclusion Criteria

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

- Lesion in femoral bone requiring surgical fixation
- Chemotherapy agents (cytotoxic, or molecularly targeted agents) used within the period of time commencing 2 weeks prior to radiation, lasting until 1 week after the last fraction for patients randomized to SABR.
- Serious medical comorbidities precluding radiotherapy. These include interstitial lung disease in patients requiring thoracic radiation, Crohn's disease in patients where the GI tract will receive radiotherapy, and connective tissue disorders such as lupus or scleroderma.
- Substantial overlap with a previously treated radiation volume. Prior radiotherapy in general is allowed, as long as the composite plan meets dose constraints herein. For patients treated with radiation previously, biological effective dose calculations should be used to equate previous doses to the tolerance doses listed below. All such cases should be discussed with the local and study PI.
- Concurrent malignant cancer, or history of malignant cancers within the past 5 years
- Malignant pleural effusion
- Inability to treat all sites of disease
- Maximum size of 5 cm for lesions outside the brain, except:
  - Bone metastases over 5 cm may be included, if in the opinion of the local PI it can be treated safely (e.g. rib, scapula, pelvis)
  - Any brain metastasis >3 cm in size or a total volume of brain metastases greater than 30 cc
- Clinical or radiologic evidence of spinal cord compression, or epidural tumour within <2 mm of the spinal cord. Patients can be eligible if surgical resection has been performed, but the surgical site counts toward the total of up to 8 lifetime metastases (see section 3.2).
- Dominant brain metastasis requiring surgical decompression
- Pregnant or breastfeeding women

4.3. Subject Withdrawal Criteria

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

If a subject is removed or withdrawn from the study, the clinical and laboratory assessments and evaluations that would have been performed at the **Study Completion/Early Termination Visit (see Section 4.8)** should be obtained, if possible. The **Study Termination** and **Participant Withdrawal** forms must also be completed in REDCap.

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.

Subjects withdrawn or discontinued can be replaced at the discretion of the sponsor-investigator/Study Principal Investigator.

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

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 12.2 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/serious adverse events, and follow-up.

4.6. Ability to tolerate current treatment

Patients 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.

4.7. Biopsy/ Blood banking

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

Biospecimen Collection (participating sites only)

Blood sample collection for the translational aim must take place on Monday, Tuesday, Wednesday or Thursday such that biospecimens requiring immediate overnight shipping (Circulating Tumour Cells) can be received and processed quickly, without samples sitting unprocessed over a weekend.

Biospecimen requirements are summarized in Table 3.

Table 3: Specimens Required for Biomarker Studies

Specimen	Sample Type	Timing	Specimen Collection Details	Shipping
Peripheral blood	CTCs	3 time-points	Collected in CellSave® tubes for immediate (within 24h) shipping. Stable at room temperature during transport.	Overnight shipment to LHSC
	PBMCs	3 time-points	Collected in Cell-Free DNA BCT ®tubes. Once PBMC extracted, stored at participating institution (-80°C).	Annual batch-shipment on dry ice to Amsterdam UMC
	ctDNA	3 time-points	Collected in Cell-Free DNA BCT ® tubes for immediate plasma separation. Once extracted, plasma stored at participating institution (-80°C).	Annual batch-ship on dry ice to Molecular Genetics Lab, LHSC

CTC, circulating tumour cell; PBMC, peripheral blood mononuclear cell; ctDNA, circulating tumour deoxyribose nucleic acid; LHSC, London Health Sciences Centre; PaLM, Pathology and Laboratory Medicine;

Laboratory Support and Shipping

Each participating institution will require an on-site laboratory for peripheral blood sample processing. This laboratory must also have freezer storage (-80°C and liquid nitrogen). The protocols for collection and processing of peripheral blood, including required equipment and reagents, are provided in the **SABR-COMET-3 Laboratory Manual**. All shipping costs will be covered by the lead translational aim site (London Health Sciences Centre), and an additional small stipend will be provided to cover laboratory time. A 'biomarker studies kit' containing collection tubes and pre-paid shipping labels will be sent to each participating institution to be retained by the personnel responsible for biospecimen collection (Figure 2).

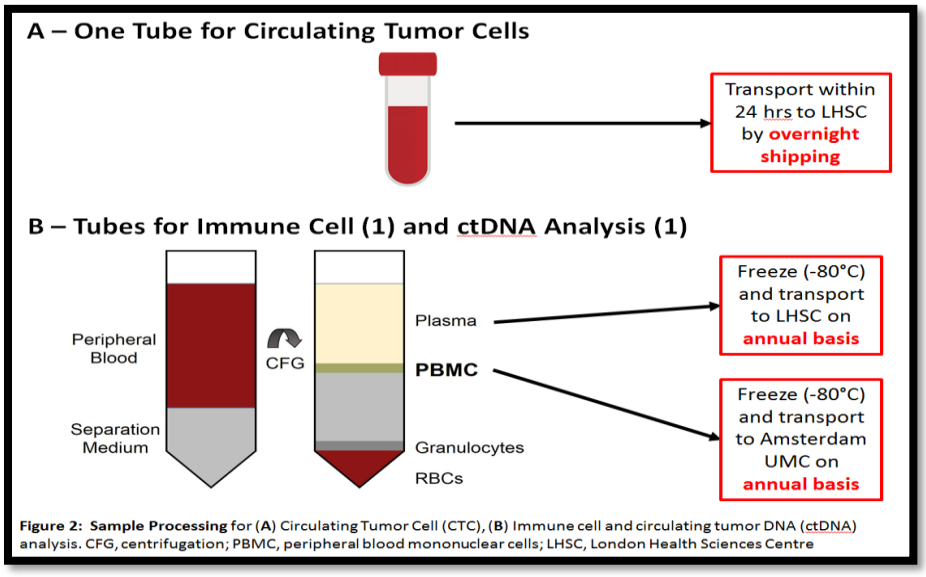


Figure 2: Sample Processing for (**A**) Circulating Tumor Cell (CTC), (**B**) Immune cell and circulating tumor DNA (ctDNA) analysis. CFG, centrifugation; PBMC, peripheral blood mononuclear cells; LHSC, London Health Sciences Centre

4.8 Schedule of Activities

PRE-TREATMENT (BASELINE) EVALUATION (NO EXCEPTIONS TO TIMELINES)

- History and Physical Examination **within 6 weeks prior to study enrollment**
  - Including prior cancer therapies and cancer-specific concomitant medications (for example, systemic therapy such as immunotherapy, hormone therapy and/or chemotherapy drugs and regular/supporting medications such as anti-emetics).
- **Restaging within 8 weeks prior to randomization, and within 12 weeks prior to treatment if randomized to SABR:**
  - **Brain**: CT or MRI for tumour sites with propensity for brain metastasis. All patients with brain metastases at enrollment, or previously, require an MRI.
  - **Body**: 18-FDG PET/CT imaging is strongly recommended, except for tumours where FDG update is not expected (e.g. prostate, renal cell carcinoma). PSMA-PET or choline-PET is recommended for prostate cancer. In situations where a PET scan is unavailable, or for tumours that do not take up radiotracer, CT chest/abdomen/pelvis with bone scan is required at baseline. CT Neck as clinically indicated.
  - **Spine**: MRI required for patients with vertebral or paraspinal metastases, though the MRI can be limited to the involved segment, including at least the involved vertebral body(ies) plus 2 vertebral bodies above and below, where applicable.
- Pregnancy test for women of child-bearing potential **within 4 weeks of RT start date**
- Complete Blood Count (CBC) **within 8 weeks prior to randomization**
- Pulmonary function tests, if previously documented poor lung function, treating near lung, and at discretion of investigator
- Liver function tests, if poor liver function, treating near liver, and at discretion of investigator

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

Assessment	Screening/ Baseline Staging Investigations	Enrollment/ Randomization	Treatment	€Follow-Up 6 Week (+/- 3 Weeks)	Follow-Up 3 Month (+/- 3 weeks	Follow-Up 6 Month (+/- 6 weeks)	Follow-Up 12 Month (+/- 6 weeks)	Follow-Up 18 Month (+/- 6 weeks)	Follow-Up 24 Month (+/- 6 weeks)	Follow-Up 36 Month (+/- 6 weeks)	Follow-Up 48 Month (+/- 6weeks)	Follow-up 60 Month (+/- 6 weeks) or Early Termination
Inclusion/Exclusion Criteria	X											
Medical History	X			X	X	X	X	X	X	X	X	X
Physical Examination	X											
Hematology (CBC, and PFTS, LFTS, if applicable)	X											
Informed Consent	X											
¥Pregnancy Test	X	£X										
Medical Imaging	X* (see annotations below and refer to sections 3.2 and 4.8)	£X			X** (see annotations below and refer to section 7.0)							
Enrollment/ Randomization		X										
Concomitant Medications		X		X	X	X	X	X	X	X	X	X
QoL (BPI, FACT-G or FACT subscale scoring (see table)) **All Sites**		X		X	X	X	X	X	X	X	X	X
EQ-5D-5L **Canadian Sites Only**		X			X	X	X	X	X	X	X	X
Provider-Reported Resource Utilization **All Sites**					X	X	X	X	X	X	X	X
Patient Reported Resource Utilization **Canadian Sites Only**					X	X	X	X	X	X	X	X

Assessment	Screening/ Baseline Staging Investigations	Enrollment/ Randomization	Treatment	€Follow-Up 6 Week (+/- 3 Weeks)	Follow-Up 3 Month (+/- 3 weeks	Follow-Up 6 Month (+/- 6 weeks)	Follow-Up 12 Month (+/- 6 weeks)	Follow-Up 18 Month (+/- 6 weeks)	Follow-Up 24 Month (+/- 6 weeks)	Follow-Up 36 Month (+/- 6 weeks)	Follow-Up 48 Month (+/- 6weeks)	Follow-up 60 Month (+/- 6 weeks) or Early Termination
Specimen Collection (Participating sites only)		X (prior to treatment)			X							X (or at progression)
CT Planning		X										
Quality Assurance/ Peer Review of Contours		X										
Radiation Treatment			X									
Toxicity Assessment				X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X

* At baseline a CT C/A/P + Bone scan should be ordered for staging if PET is not carried out. CT neck at baseline may be done as clinically indicated.

**During follow-up extra imaging outside of study schedule is allowed per discretion of the study doctor. Either CT C/A/P or PET is required. If PET is done, CT C/A/P is not required (or vice versa). Bone scans for follow-up visits are to be ordered as clinically indicated (ex. for patients with bone mets) and as per discretion of the oncologist. CT neck in follow-up is optional and based on the oncologist's discretion. Follow-up MRI is required only for anatomical sites which required MRI for study entry (see section 3.2). All imaging is optional for prostate cancer patients with PSA < 5 for follow-up visits. If patient develops disease progression, post-progression imaging will be per standard of care. See also section 7 for follow-up imaging requirements.

£Repeat scan/test only if initial scan/test is outside valid timelines listed below

€At discretion of study doctor for patients randomized to Arm 1 (SOC)

¥ Urinalysis or serology – per institutional guidelines.

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 +/- 6 weeks, from target follow-up date, in order to align with scans** used to assess response to systemic therapy.

Physical and Medical History will be valid <u>within 6 weeks prior to enrollment.</u>
Imaging and test results will be valid for <u>8 weeks prior to enrollment,</u> and <u>12 weeks prior to treatment for patients randomized to SABR</u>.
Pregnancy test results will be valid for <u>4 weeks prior to treatment</u>.

QoL Questionnaires Per Metastatic Site

Site	Questionnaires
Adrenal / Pancreas	FACIT-Abdominal
Bone / Spine	FACT-General + BPI
Brain	FACT-Brain
Liver	FACT-Hep/Liver (Hepatobiliary)
Lung	FACT-Lung
Lymph Node/Soft Tissue Abdominal area	FACIT-Abdominal
Lymph Node/Soft Tissue Head & Neck area	FACT-Head & Neck
Lymph Node/Soft Tissue Male Pelvis area	FACT-Prostate
Lymph Node/Soft Tissue Female Pelvis area	FACT-Cervix
Lymph Node/Soft Tissue Chest/Lungs	FACT-Lung
Other	FACT-General

5. Subject Treatment Plan

5.1. Trial Treatment Summary

5.1.1. Standard Arm (ARM 1)

Radiotherapy for patients in the standard arm should follow the principles of palliative radiotherapy as per the individual institution, with the goal of alleviating symptoms or preventing imminent complications. Patients in this arm should not receive stereotactic doses or radiotherapy boosts. Recommended dose fractionations in this arm will include 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions. Patients who decline or who do not receive palliative RT should still be followed and complete all quality of life questionnaires.

Systemic therapy will be pre-specified based on the standard of care approach for that patient, and it may include systemic therapy (cytotoxic, targeted, hormonal, or immunotherapy) or observation. See section 5.2.1.6 for the timing of systemic therapy.

5.1.2. Experimental – SABR (ARM 2)

Table 1 presents the dose and fractionations to be used in delivery of SABR. All doses are prescribed to the periphery of the planning target volume (PTV).

Table 2 Dose and fractionations by site [secondary options in square brackets]

Tumour Location	Description		Total Dose (Gy)	Number of fractions	Dose per fraction (Gy)	Frequency
Lung	Tumours 5 cm or less surrounded by lung parenchyma		48 Gy [54 Gy]	4 [3]	12 Gy [18 Gy]	Daily, or Every second day
	Within 2 cm of mediastinum or brachial plexus		60 Gy	8	7.5 Gy	Daily
Bone	Any bone		35 Gy [24 Gy]	5 [2]	7 Gy [12 Gy]	Daily
Brain	Stereotactic lesions (no whole brain RT)	< 2cm	20-24 Gy	1	20-24 Gy	Once
		2-3 cm	18 Gy	1	18 Gy	Once
	Metastases only		35 Gy	5	7 Gy to PTV	Daily
	Whole brain + Metastases		35 Gy to metastases 20 Gy whole brain	5	7 Gy to PTV 4 Gy WBRT	Daily
Liver			54 Gy	3	18 Gy	Every second day
Adrenal / Pancreas			40 Gy [35 Gy]	5	8 Gy [7 Gy]	Daily
Lymph Node/Soft Tissue			40 Gy	5	8 Gy	Daily

5.1.2.1 Immobilization

Treatment will be set up using reproducible positioning and verified using an on-line protocol for all patients in this study. Immobilization may include a custom immobilization device, such as thermoplastic shell or vacuum bag, as per individual institutional practice when delivering SABR. Some centers do not use immobilization devices and have demonstrated high degrees of accuracy; this is acceptable in this study.

5.1.2.2 Imaging/Localization/Registration

All patients in Arm 2 will undergo planning CT simulation. 4-dimensional CT will be used for tumours in the lungs, liver, or adrenals. Axial CT images will be obtained throughout the region of interest. **For centres using stereotactic radiosurgery platforms, real-time tumour tracking and orthogonal imaging systems are permitted.**

5.1.2.3 4D-CT Procedures

For patients undergoing 4D-CT, medical physics will review the 4D-CT images and will perform the following quality assurance procedures according to institutional guidelines:

i) Ensure all end inspiration (0%) tags exist and are in the right place. This ensures image integrity.
ii) If the quality of the 4D-CT images is not sufficient (determined by Physics), then standard 3D-CT will be performed on the fast helical CT or Untagged Average CT.
iii) Motion measurements in all 3 directions are performed:
    1) If the motion is less than or equal to 7 mm and the good quality images exist, then treatment planning may be performed on the Untagged Average CT with the 50% or 60% phase (End Expiration) and the 0% phase being fused to it. This will define the IGTV.
    2) If the motion is greater than 7 mm in any one direction, then respiratory-gated radiotherapy can be considered. In this case, treatment planning will be performed on a subset average CT dataset (usually labeled either 30%-60% Avg CT or 40%-70% Avg CT) generated by Physics. This is an average CT over the intended gated interval. Therefore, the GTV that is delineated on this scan will incorporate residual motion in the intended gated interval. The 0% phase will also be fused to this dataset. The PTV for planning will include the GTV delineated on the subset average CT plus margins for microscopic extension (Physician's discretion) and setup uncertainty. The GTV_0% should also be delineated and combined with the GTV delineated on the subset average CT to define an additional volume labeled IGTV_CBCT. This contour may be used for image registration with CBCT only.

5.1.2.4 Volume Definitions (Arm 2)

For all lesions, the gross tumour volume (GTV) will be defined as the visible tumour on CT and/or MRI imaging +/- PET. No additional margin will be added for microscopic spread of disease (i.e. Clinical Target Volume [CTV]=GTV). For bone lesions, CTV of 3-5mm will be

allowed. For vertebral lesions, anatomic approach will be taken as per International Spinal consortium guideline[17,18].
An anatomic approach is taken to the CTV based on where the disease within the spinal segment is located. The rules for CTV are as follows:

1. If the vertebral body is involved with GTV then the entire vertebral body is taken as CTV.
2. If the ipsilateral pedicle and/or transverse process has GTV then the entire ipsilateral posterior segment (pedicle, lamina and transverse process) ±the spinous process is taken into the CTV. The inclusion of the spinous process is per the discretion of the radiation oncologist.
3. If the ipsilateral pedicle, lamina, and/or transverse process has GTV, then the entire ipsilateral posterior segment (pedicle, lamina, and transverse process) plus the spinous process is taken into the CTV
4. If bilateral involvement of the pedicle and/or transverse process with GTV, then the posterior segment anatomy ± the spinous process is taken into the CTV. The inclusion of the spinous process is per the discretion of the radiation oncologist.
5. If bilateral involvement of the pedicles and lamina, and/or transverse process with GTV, then the entire posterior segment anatomy is taken into the CTV, including the spinous process.
6. If the spinous process is involved with GTV alone then the bilateral lamina ± pedicles are to be taken into the CTV.

The International Spinal Consortium Guideline is a reference for CTV delineation and can be adhered to as described[17,18].

In the case of epidural disease, a 5 mm anatomic margin (excluding the spinal cord) beyond the GTV may be used within the epidural compartment including in the cranio-caudal direction. A circumferential CTV as per a donut-based CTV is allowed and encouraged in the case of epidural disease at the discretion of the treating radiation oncologist. If paraspinal disease present, a minimum 5 mm CTV margin may be applied beyond the GTV.

A Planning Target Volume (PTV) margin of 2-5 mm will be added depending on site of disease, immobilization, and institutional set-up accuracy: 2-3 mm margins should be used for spinal stereotactic treatments, 0-2 mm for brain tumours, and 5 mm for other sites.

Targets should be named based on the organ involved, and numbered from cranially to caudally. For example, in a patient with 3 lung lesions, there would be: GTV_lung_1, GTV_lung_2, and GTV_lung_3, and corresponding PTV_lung_1, PTV_lung_2_, and PTV_lung_3, representing the lesions from superior to inferior.

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. Alternatively, the thecal sac may be used as the PRV. For radiosurgery platforms, a PRV margin of 1 mm is permitted for the spinal cord.

Organ At Risk (OAR) Doses

OAR doses are listed in **Appendix 1**. OAR doses may not be exceeded except in the case of chestwall / ribs. In cases where the PTV coverage cannot be achieved without exceeding OAR doses, the PTV coverage is to be compromised. All serial OARs within 5 cm of the PTV must be contoured (partial organ contours allowed); for parallel organs (liver, lung, etc.) within 5cm of PTV, the whole organs need to be contoured. This should be tested for each PTV by creating a 5 cm expansion to examine which OARs lie within that expansion.

Treatment Planning

Treatment can be delivered using static beams (either 3D-conformal radiotherapy or intensity-modulated) or rotational therapy (volumetric modulated arc therapy, or tomotherapy).
Dose constraints may not be exceeded (except chestwall/ribs). If a dose constraint cannot be achieved due to overlap of the target with an organ at risk, the fractionation can be increased or the target coverage compromised in order to meet the constraint. In cases where the target coverage or dose must be reduced, the priority for dose coverage is the GTV (e.g. attempt to cover as much of the GTV as possible with the prescription dose). **All such cases of dose reduction or target coverage compromise must be approved by the local PI prior to treatment.** For vertebral tumours, note that the spinal cord constraints apply to the PRV.

For all targets, doses should be prescribed to 60-90% isodose line surrounding the PTV, and all hotspots should fall within the GTV. 95% of the PTV should be covered by 100% of the prescription dose, and 99% of the PTV should be covered by 90% of the prescription dose.

Doses must be corrected for tissue in homogeneities. Several non-overlapping 6/10 MV beams (on the order of 7-11 beams) or 1-2 VMAT arcs combined possibly with a few non-coplanar beams should be utilized. Non-coplanar beams can be used to reduce 50% isodose volumes.

The number of isocentres is at the discretion of the treating physician, physicists, and dosimetrists. Generally, metastases can be treated with separate isocenters if they are well-separated.

The scheduling and sequence of treating each metastasis is at the discretion of individual physicians, but in general should begin with the brain, due to risks associated with progression. Radiation schedule will depend on sites of tumour being treated, but generally daily or every other day for 1-3 weeks.

As CNS SRS for brain mets is offered on either arm there are no planning constraints or dosimetric submissions required for brain treatment.

5.1.2.5 Quality Assurance (Arm 2)

In order to ensure patient safety and effective treatment delivery, a robust quality assurance protocol is incorporated. The following requirements must be completed for each patient:

- Prior to treatment, each patient must be discussed at quality assurance (QA) rounds **or** be peer reviewed by a radiation oncologist with SABR expertise.

- All radiotherapy plans **must meet target dose levels for organs at risk (except chestwall/ribs)** (Appendix 1). Prior to plan approval, the dose to each organ at risk must be verified by the physicist or treating physician.
- All dose delivery for intensity-modulated plans (including arc-based treatments) will be confirmed before treatment by physics staff.

Peer review of contours may be done within centre and must follow institutional guidelines.
Acceptable documentation of peer review and approval:

- Certified copies of approvals within Radiation Therapy planning software,
- COMET-3 Quality Assurance study forms,
- Email. If email is used, all elements of the QA form must be addressed in the email, including final approval of contours.

Certified copies of approvals, email, or QA forms must be uploaded to REDCap or saved at the site.

DICOMs for SABR patients must be submitted to the Coordinating Centre before the end of the recruitment period.

5.1.2.6 Systemic Therapy

Patients treated with prior systemic therapy are eligible for this study, however, no chemotherapy agents (cytotoxic, or molecularly targeted agents) are allowed within the period of time commencing 2 weeks prior to radiation lasting until 1 week after the last fraction. Hormonal therapy is allowed. Use of chemotherapy schemes containing potent enhancers of radiation damage (e.g. gemcitabine, adriamycin/doxorubicin, bevacizumab) are discouraged within the first month after radiation.

5.1.2.7 Further radiotherapy for progressive disease at new metastatic sites

Patients in Arm 1 who develop new, untreated metastatic deposits should be treated with standard-of-care approaches. SABR to those sites is not permitted, except for unique scenarios where it would be considered standard of care (e.g. all disease controlled on systemic therapy with a newly developed brain metastasis). Apart from brain metastases, treatment of 'oligo-progression' with SABR is not permitted.

Patients in Arm 2 who develop new, untreated metastatic deposits should be considered for SABR at those sites, if such deposits can be treated safely with SABR, and if the treating institution offers SABR for that body site. If SABR is not possible, then palliative RT can be delivered as clinically appropriate. Data collection for progression at new sites is not required under this protocol

5.1.2.8 Quality Assurance for Centres Joining Study

Prior to opening the study, each participating research centre will be required to send to the Study Principal Investigator a mock treatment plan for the anatomic sites that will be treated (e.g. Lung, brain, liver, adrenal), to ensure that the treatment plans are designed in compliance with the protocol. The local principal investigators will provide pertinent CT datasets. Each participating research centre can choose which tumour sites will be treated at their individual centre (i.e. some centres may only choose to treat a subset of the eligible metastatic sites). Sites that have prior accreditation for SABR through a clinical trial (e.g. SABR-COMET, or organ-specific SABR trials) are exempt from this requirement for the organ sites that have been accredited in those trials.

5.1.3 Duration of Study

Per section 3.3, this study is expected to be 11 years in duration.

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. Source data must be printed and retained in the subject's research file/source documentation.
- The investigator must permit study-related monitoring, audits, REB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the **SABR-COMET-3 Monitoring Plan**.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- The 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.

Data Sharing
Protocol Data from this study will be pooled with the pending EORTC trial OligoRARE, a randomized trial specifically looking at the impact of SABR in patients with oligometastases from less-common tumour histologies. Anonymized data from patients with non-breast, non-prostate, non-lung and non-colorectal histologies will be shared with EORTC investigators.

5.2.1 Subject Reported Outcomes – Questionnaires

5.2.1.1 Functional Assessment of Cancer Therapy:
General (FACT-G) / *FACT sub-scale (site specific) / Brief Pain Inventory (BPI): data will be used to measure patient reported Quality of life

*FACT sub-scales:
-FACIT-Abdominal Symptoms
-FACT-Brain
-FACT-Cervix
-FACT-Head and Neck
-FACT-Hepatobiliary (Liver)
-FACT-Lung
-FACT-Prostate

Both paper and electronic versions are available. Subjects and Sites may use either or both collection methods as appropriate.

5.2.1.2 EuroQol-5 Dimensions 5-Level (EQ-5D-5L) (Canadian sites only):
Responses to the EQ-5D-5L will generate a measure of individual's preference for a health state multiplied by the length of time in that health state to yield a QALY [21-23]. QALYs will be combined with resource utilization for the cost utility analysis. Canadian weights for the EQ-5D-5L will be applied[24,25].

Both paper and electronic versions are available. Subjects and Sites may use either or both collection methods as appropriate.

5.2.1.3 Patient- and Provider-Reported Resource Utilization Forms:
The Patient-Reported Resource Utilization Form (Canadian sites only) will capture the number of units of key resources reported by the subject from time of randomization to death or trial cessation, whichever occurs first. The Provider-Reported Resource Utilization Form (all sites) will capture units of key resources extracted from centre and trial administrative databases. Key resources include number of cycles of further chemotherapy/systemic therapy, targeted- and immune-therapies, number of Emergency Room visits, number of hospital admissions, and physics, radiation oncologist, radiation therapist, nurse, and treatment unit time. Direct medical

costs and costs per unit of resource consumption will be established using provincial fee schedules (e.g. BC Medical Services Plan (MSP), Ontario Health Insurance Plan (OHIP), Nova Scotia Pharmacare) and provincial program data (e.g. New Drug Funding Program and the Ontario Drug Benefit (ODB) Program and BC Cancer Provincial Systemic Therapy Program)

Both paper and electronic versions are available. Subjects and Sites may use either or both collection methods as appropriate.

5.2.2 Records Retention

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. 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

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

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

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, adriamycin/doxorubicin, bevacizumab) 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 (i.e. medications prescribed by a physician to reduce side effects of cancer/treatments) must be documented at registration and at all study follow-up visits.

Concomitant medications must be recorded on the **SABR-COMET-3 Concomitant Medication Form**, which is a cumulative form to be updated throughout the study.

5.4 Co-enrolment

Enrollment in other studies **may** be permitted. Investigators **must** check with 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. 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

In general, dose modifications are not allowed, but PTV undercoverage is allowed and already described in 5.1.2.4 Volume Definitions (Arm 2) - Treatment Planning section. If a dose modification is thought to be required/necessary, the modification **must** be discussed and approved **by both the local Site PI and the Study PI.**

6.2 Interruptions (Arm 1 and Arm 2)

Unscheduled treatment interruptions greater than 24 hours in duration will be considered minor deviations for either arm. Unscheduled treatment interruptions greater than 36 hours in duration will be considered major deviations in the intervention Arm 2. Both deviations must be reported to the Study PI immediately.

6.3 Missed Doses (Arm 2 (SABR))

Missed doses, defined as omission of 1 or more fractionation(s), are major violations and not allowed for the intervention Arm 2. Missed doses must also be reported as deviations to the Study PI immediately.

7. Assessment of Efficacy

Clinical follow-up appointments will occur at 6 weeks, 3 months, and then every 6 months (from treatment end date) for the first two years, and annually for years 3-5, and may be conducted via telephone or videolink. Follow-up visits for SABR patients should be scheduled from SABR treatment end date. Follow-up visits for all SOC patients, including those who do not receive any treatment, should be scheduled from randomization date. At each visit, a medical history will be conducted by the oncologist or a delegated family physician (e.g. if patient is followed over videolink), and CTCAE[26] toxicities and Eastern Cooperative Oncology Group (ECOG) score recorded. The FACT-G or subscale, EQ-5D-5L Quality of life, and resource utilization questionnaires are to be completed at each visit, remotely (e.g. by phone, videolink, or mail), or the patient can complete these questionnaires at home (online using REDCap or on paper and mailed to investigator).

Follow-Up Imaging should be ordered based on site(s) of metastasis(ses) and imaging ordered for staging. General guidelines:

- CT Brain – as clinically indicated, if there is a propensity for brain metastases (if brain MRI not carried out)
- MRI Brain – as clinically indicated, if there is a propensity for brain metastases (if brain CT not carried out)
- MRI (sites other than head) – if MRI was required for study entry (and in addition to CT C/A/P or PET)
- CT C/A/P– For all patients at all imaging FU timepoints (If PET not carried out)
- Bone scan - as clinically indicated and as per discretion of the investigator (ex. follow-up of patient with a bone met)
- PET – For all patients at all imaging FU timepoints if CT C/A/P not carried out.
- CT neck - optional and based on the oncologist's discretion.

CT brain (or MR brain [as applicable]), MRI (as applicable), and/or CT chest, abdomen and pelvis (CT C/A/P) or PET will be carried out at 3 and 6 months and repeated every 6 months, for the first 2 years, then every 12 months until 5 years have elapsed. Bone scan as clinically indicated and as per discretion of oncologist. Brain imaging can be omitted for histologies without a propensity for brain metastases (e.g. prostate). CT neck in follow-up is optional and based on the oncologist's discretion. 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, and pelvis (and neck where applicable); brain imaging would still be required for histologies with a propensity for brain metastases (definition of propensity for brain metastases to be left to the treating investigator). If PSMA-PET or PET-CT was used for staging, but is not available for follow-up, CT C/A/P can be ordered for follow-up assessments (i.e. prostate cancers). ***Patients with prostate cancer who have a PSA below 5 may omit all follow-up imaging requirements, regardless of the location/number of metastases.***

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 +/- 6 weeks, from target follow-up date, in order to align with scans used to assess response to systemic therapy.***

Biomarker Methodology: The Liquid Biopsy

To evaluate potential biomarkers in a clinical setting, the use of a "liquid biopsy" is less invasive and more practical alternative to repeat biopsies. A liquid biopsy refers to sampling of peripheral blood to isolate and characterize circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), and/or circulating host immune cells, among others[27]. Liquid biopsy is an ideal sampling technique in this clinical trial because biopsy of metastatic lesions is not always possible, and unlike metastectomy, SABR does not inherently yield tissue. Moreover, there is evidence that post-SABR anti-tumour immune activation can be detected in the peripheral blood[27] and that tumour necrosis (the immunogenic cell death mechanism associated with SABR) is associated with greater ctDNA concentrations, [30] thus making liquid biopsy a rational means by which to assess potential biomarkers longitudinally.

Despite its many potential advantages, liquid biopsy does have some drawbacks, including the fact that discordance has been observed between genotyping via ctDNA versus tumour tissue; however, this may merely reflect clonal or temporal heterogeneity.[27]

8. Assessment of Safety

8.1 Specification of Safety Parameters

8.2 Recording and Reporting of Adverse Events (AEs)

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 Serious Adverse Event (SAE) and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the 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 intervention until completion of all follow-up visits.

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

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

8.2.2 Method for Detecting AEs and SAEs

Definitions
An *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/treatment:

- 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 (excluding hospital admissions for scheduled elective surgery and admissions for palliative or terminal care)
- Is a congenital anomaly/birth defect

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.

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).

Expected events are distinguished from unexpected events on a case-by-case basis, at the discretion of the radiation oncologist.

Causality

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 possibly related and 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) v5.0 grading scale[26].

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

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[33].

Grade 2 or higher toxicities that are possibly, probably, or definitely related to any cancer treatment must be documented and reported as AEs/SAEs for both arms.

All Grade 3 or higher toxicities, related or not to cancer treatment, must also be documented, though start and stop dates do not need to be collected for toxicities considered to be unrelated or unlikely related to cancer treatment.

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

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.

Immediately Reportable Serious/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, and further reported to the REB per institutional guidelines. 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 a SAE Report form and in REDCap as well.

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

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

8.3 Follow-up of Subjects after Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each 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).

8.4 Pregnancy

Details of pregnancies will not be collected.

9. Statistics

9.1 Statistical Methods

Patients will be analyzed in the groups to which they are assigned (intention-to-treat).

Survival Endpoints
PFS and OS will be calculated using the Kaplan-Meier method with differences compared using the stratified log-rank test. Pre-planned subgroup analysis will occur based on the stratification factors, and also based on the use of immunotherapy vs. non-immunotherapy systemic agents. 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.

Secondary Endpoints
Quality of life at 6 months will be measured using FACT, Cancer Specific Questionnaires, and EQ-5D-5L scores, with differences between groups tested using the Student's t-test[21-24,35]. Differences in rates of grade 2 or higher toxicity between groups will be tested using the Fisher's Exact Test.

Cost Utility Analysis (CUA)
A CUA will be conducted in line with the Canadian Agency for Drugs and Technologies in Health (CADTH) Guidelines for the Economic Evaluation of Health Technologies[36,37]. Non-parametric bootstrapping will be used to estimate the 95% confidence intervals and to construct a cost-effectiveness acceptability curve. Sensitivity analysis will be conducted by varying the major drivers of costs. All costs will be adjusted to a base year using the healthcare component of the Statistics Canada Consumer Price Index[38] to adjust for price inflation over time. Subsequent incremental cost per unit of OS improvement using OS outcomes will be explored. Although Canada has a single-payer health insurance system, the provincial and territorial governments are responsible for health care administration and delivery. Our analyses will be undertaken from the perspectives of the BC and Ontario provincial Ministries of Health as we expect these provinces to accrue the highest number of patients. We will gain consent from all trial participants to prospectively assess their patient-level records pertaining to the frequency of hospital admissions and the use of targeted- and immunotherapies. We will use the resource costing method whereby utilization data are collected from existing data sources and then multiplied by unit costs.

Interim Analyses
There will be 3 interim analyses. The data and safety monitoring committee (DSMC) will conduct the first interim analysis once 50 patients are accrued. For this analysis, the DSMC will be blinded to the identity of each treatment arm, but OS data will be presented for each arm, and treatment doses and volumes will be presented for SAEs reviewed. There are two planned interim analyses for efficacy in addition to the final analysis. The two interim analyses are expected to be carried

out when the total number of observed study deaths reaches 40 and 65, thus treatment details will be reviewed to determine plausible causation of toxicities. As such, interim efficacy analyses will not be blinded. The DSMC will recommend stopping the trial if there is an OS difference that is statistically significant with a threshold of $p<0.001$ using the log-rank test. The final analysis is expected to be carried out 3 years after the enrollment of the last subject.

Circulating Tumour Cell Analysis

Rationale

Circulating tumour cells have repeatedly demonstrated their utility as a clinical prognostic metric. Prospective clinical studies have provided evidence that CTCs are prognostic in metastatic breast, prostate, and colorectal cancer, whereby increasing concentration correlates with oncologic outcomes such as treatment response and survival.[27-30] Recently, the largest pooled CTC analysis to date revealed that CTC enumeration identifies an indolent subgroup of metastatic breast cancer patients (Stage $IV_{indolent}$) with improved survival, independent of treatment or molecular subtype[39]. The role of CTCs in oligometastatic disease has not been studied, yet the sub-population with slowly-progressing natural history may overlap with the clinical definition of oligometastasis. Thus, CTCs may represent a useful prognostic and/or predictive biomarker and their evaluation in this setting is warranted.

Analysis

A peripheral blood sample will be collected at each participating institution into provided CellSave blood collection tubes (Menarini Silicon Biosystems; preferred) or Cell-Free DNA BCT® blood collection tubes (Streck) which stabilize CTCs for 96 h at room temperature. Samples will then be prepared for CTC analysis using the CellSearch system (Veridex, Inc.) in the London Health Sciences Centre (LHSC). Participating institutions will ship samples within 24h to LHSC for processing and CellSearch analysis.

Host Immune Cell Analysis

Rationale

The role of the host immune system in establishing a prohibitive or permissive microenvironment for metastatic colonization is increasingly well-established: while activation of cytotoxic T-lymphocytes is thought to inhibit metastases, regulatory T-lymphocytes can conversely exhaust/de-activate anti-tumour immunity, thus having the opposite effect[40]. Additionally, recent evidence suggests that natural killer cells contribute to non-specific immune surveillance to create an inhospitable milieu for the establishment of metastatic colonies.[31] Furthermore, as evidenced by the successful application of immune-checkpoint inhibition in treating metastatic cancer, the modulation of the host immune system can dramatically impact the extent of metastasis. Finally, both pre-clinical and clinical data demonstrate that immune cell activity can also be modulated by SABR,[41] an effect that can be monitored in peripheral blood via analysis of circulating immune cells following radiotherapy.[28] SABR may also effect a so-called abscopal (out-of-field) response, thereby improving control of metastatic disease[42]. Given the important role of immune surveillance for metastasis, its therapeutic modulation in the setting of metastatic disease, and its

interplay with SABR, evaluating the importance of host immunity in the context of oligometastasis ablation is warranted to explore useful predictive and/or prognostic biomarkers.

Analysis
We aim to analyze peripherally circulating immune cells for expression of surface antigens that are reflective of immune activation or exhaustion/suppression. The analysis itself will be conducted by the Amsterdam UMC. Samples will be collected and stored at each participating institution as per the Laboratory Manual and stored at -70 ºC-80ºC will subsequently be shipped, on an annual basis, on dry ice to VU Amsterdam for further processing and Fluorescence-activated cell sorting (FACS) analysis.

Tumour DNA Analysis
Rationale:
Recent studies utilizing contemporary genomic analysis techniques have identified individual gene-level alterations (e.g., mutations and copy-number variations) as well as genome-scale metrics (e.g., tumour mutational burden and percent genomic copy-number alteration) that correlate with metastatic disease and poor outcomes[30-33]. Perhaps most informatively, multi-region sequencing of primary tumours and paired metastases has permitted phylogenetic analysis of metastasis evolution, shedding light on genetic alterations that correlate with patterns of metastatic dissemination; specifically, elect genetic alterations in the setting of renal cancer effectively differentiate a rapid, multi-site "poly-metastatic" progression from an attenuated, indolent metastatic disease course reminiscent of an oligometastatic natural historyhistory[32]. These large-scale studies have performed whole-genome sequencing in each patient, an approach that is not currently practical or cost-effective in the clinical setting. However, curating the findings of these large-scale analyses to develop a targeted approach using a panel-based subset of frequently-altered genetic loci will permit a more focused yet rationally-based evaluation of oligometastatic tumour DNA, akin to the approach taken by Abbosh *et al.* [30]

Analysis:
The plasma fraction containing circulating tumour DNA (ctDNA) will be isolated from peripheral blood collected at the above-mentioned timepoints as per the protocol detailed in the Laboratory Manual. Once extracted, plasma samples will be frozen at -70 ºC to -80ºC. Concentration of ctDNA to gauge feasibility for subsequent analysis will be determined prior to freezing and storage. Participating institutions will batch-ship frozen samples on dry ice to LHSC where all samples will be stored.

9.2 Planned Subjects Enrolled

Sample Size Calculation

The results of the original SABR-COMET phase II trial demonstrated median OS of 28 months in the standard arm, 41 months in the experimental arm, and a 22% improvement in 5-year OS. Based on these results, this phase III trial initially aimed to detect a Hazard Ratio of death of 0.66 in the experimental arm compared to the standard arm (i.e. a 40% reduction in the hazard rate of death). A 5-year OS of 20% had been assumed for the standard arm; the HR of 0.66 represents a 15% improvement in OS, smaller than the effect observed in the phase II trial. In order to detect this difference, with 80% power, alpha of 0.05, and an 8% dropout rate, assuming 5 years of accrual and a total trial time of 8 years, 297 patients would be required (i.e. 99 in Arm 1 and 198 in Arm 2).

Amendment June 2022:

Study sample size was increased to 330 (in Arm 1 and 220 in Arm 2)This sample size will provide 80% power to detect an improvement in median OS from 16 months to 27 months allowing for 5% dropout. This assumes 5 years of accrual and 1 year of additional follow-up.

9.3 Procedures for Reporting Deviations from the Statistical Plan

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

10. Measurement of Study Endpoints

Primary Outcome Measure:

Overall survival: Time from randomization to death from any cause [Time Frame: At approximately end of year 5 (study completion)]

Secondary Outcome Measures:

- **Side effects:** Occurrences of grade 2 or higher adverse events assessed at 6 weeks, 3 months, 6 months, and every 6 months post treatment for years 1 and 2. At approximately end of years 3, 4, and 5.
- **Progression-free survival (PFS):** Time from randomization to disease progression at any site or death. [Assessment Time Frame: At 6 weeks, 3 months, 6 months, and every 6 months post treatment for years 1 and 2. At approximately end of years 3, 4, and 5.]
- **Patient-reported quality of life (QoL)**: assessed via Functional Assessment of Cancer Therapy- General (FACT-G)/sub-scale questionnaires administered at baseline, 6 weeks, 3 months, 6 months, and every 6 months post treatment for years 1 and 2. At approximately end of years 3, 4, and 5.
- **Health-related quality of life (HRQoL):** assessed via EuroQOL Group EQ-5D-5L questionnaire administered at baseline, 3 months, 6 months, and every 6 months post treatment for years 1 and 2, and at approximately end of years 3, 4, and 5.
- **Resource Utilization:** assessed via Patient- and Provider-Reported number of hospital admissions, ER visits, systemic or radiation therapy, collected at 3 months, 6 months, and every 6 months post treatment for years 1 and 2, and at approximately end of years 3, 4, and 5.
- Correlation between candidate biomarkers of oligometastatic disease (blood- derived) and oncologic outcomes: assessed via CTC and ctDNA Enumeration/Detection at baseline, 3 months post-treatment, and at disease progression or study completion (Year 5)

10.1 Definitions

10.1.1 Overall (OS) and Progression-Free Survival (PFS)

OS and PFS will be calculated using the Kaplan-Meier method with differences compared using the stratified log-rank test. Pre-planned subgroup analysis will occur based on the stratification factors, and also based on the use of immunotherapy vs. non-immunotherapy systemic agents. 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.

10.1.2 QOL measurement after treatment

Quality of life at 6 months will be measured using FACT, Cancer Specific Questionnaires, and EQ-5D-5L scores (Health-Related Quality of Life), with differences between groups tested using the Student's t-test[21-24]. Differences in rates of grade 2 or higher toxicity between groups will be tested using the Fisher's Exact Test.

10.1.3 Toxicity

Toxicity will be measured using CTCAE v5.0[26]

10.1.4 Resource Utilization

Resource utilization will be measured using data recorded on the Patient-Reported Resource Utilization and Provider-Reported Resource Utilization forms (number of units of key resources reported by the subject from time of randomization to death or trial cessation, whichever occurs first, and units of key resources extracted from centre and trial administrative databases). Key resources include number of cycles of further chemotherapy/systemic therapy, targeted- and immune-therapies, number of Emergency Room visits, number of hospital admissions, and physics, radiation oncologist, radiation therapist, nurse, and treatment unit time. Direct medical costs and costs per unit of resource consumption will be established using provincial fee schedules (e.g. BC Medical Services Plan (MSP), Ontario Health Insurance Plan (OHIP), Nova Scotia Pharmacare) and provincial program data (e.g. New Drug Funding Program and the Ontario Drug Benefit (ODB) Program and BC Cancer Provincial Systemic Therapy Program)[35,36].

10.1.5 Biomarkers

Circulating Tumour Cells (CTCs) will be detected/enumerated using the Food and Drug Administration (FDA)- and Health Canada approved CellSearch system (Menarini Silicon Biosystems) at the London Health Sciences Centre (LHSC).

Flow cytometry will be used to detect expression of cell surface antigens on host immune cells, including cytotoxic and regulatory T-lymphocytes, that are reflective of immune activation or exhaustion/suppression (processing and analysis to be conducted by the Amsterdam University Medical Centre).

Circulating tumour DNA (ctDNA) in plasma will be quantified and undergo targeted gene sequencing to assess for candidate genetic alterations related to metastatic disease. For each biological variable quantified, the appropriate statistical analysis will be used to correlate with clinical outcomes including progression-free survival and overall survival.

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 On-Study Follow-Up form and in REDCap**.

10.4 Management Following Recurrence

Follow-up After Progression

After progression, for patients randomized to Arm 2 SABR will be encouraged for new sites at MRP discretion and institution approval, even if the number of new sites exceeds the maximum number of sites allowed at baseline.

After progression, imaging, laboratory investigations, or additional treatment (e.g. further chemotherapy) should be carried out at the discretion of the oncologist. However, the patient will need to complete follow-up visits and quality of life and resource utilization questionnaires as per the trial protocol schedule. These may be done remotely (e.g. by phone or mail) to minimize visit burden for patients. Any additional visits outside of the protocol follow-up schedule are allowed at the oncologists' discretion.

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. ***Please complete the REDCap Study Termination form for each participant completing the study.*** 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

The DSMC may stop the entire study if toxicity rates are excessive (>25% grade 3 toxicity, or >5% grade 4 or 5 toxicity), or if interim analysis indicates there is an OS difference that is statistically significant with a threshold of $p < 0.001$ using the log-rank test.

11.3 Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, etc. reasons.
- 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 that will 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 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 Investigators 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 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 the current federal regulations 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. Any institution opening this study will obtain IRB/REB approval prior to local initiation and will be responsible for maintaining approval throughout the duration of the trial. Principal Investigators must provide evidence of IRB/REB approval on an annual basis.

The Principal Investigators will be responsible for the following:

- Obtaining local Institutional Review Board (IRB) / Research Ethics Board (REB) approval
- Providing written summaries of the status of the study to the REB annually or more frequently in accordance with the requirements, policies, and procedures established by the REB
- 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

Participating sites must receive pre-approval from the Study Principal Investigator for any amendments to the protocol.

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 per BC Cancer and/or institutional SOPs.

12.2. Informed Consent Process

The investigator or delegate 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 investigator or delegate will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the REB or study center.

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 patient source documents.

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

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

12.3. 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 and their representatives, representatives of the IRB/REB, and regulatory agencies). The subject's name will not be used in any public report of the study.
Include all measures to be taken to comply with the applicable rules on protection of personal data and any relevant information on measures to be taken in case of a data security breach.

Subjects will be assigned a unique identifier by the sponsor. 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 if any 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.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate REB members, and by inspectors from regulatory authorities.

12.4. Committees Structure

The Data Safety Monitoring Committee (DSMC) will review data relating to safety and efficacy, conduct and review interim analyses, and ensure the continued scientific validity and merit of the study. There will be 3 interim reviews conducted by the DSMC for the purpose of monitoring study conduct and assessing patient safety. See sections 1.1 Synopsis (Formal Stopping Rules) and Section 9.1 Statistical Methods for details regarding DSMC interim analyses.

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 sponsor 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

12.6. Premature Termination or Suspension of Study

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the REBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

12.7. Publication Policy

Upon completion of this project, the results will be published in a peer-reviewed journal and presented at one or more conferences. Investigators agree to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor 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 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. Accrual at each center and the amount of individual contribution, including study design, patient accrual, and data analysis will also factor in to authorship.

12.8. Financial Support

This trial is funded by the BC Cancer Research Foundation, the Canadian Institutes for Health Research (CIHR), and Varian Medical Systems. The funding agencies are not directly involved in data collection or analysis.

12.9. Trial Management

The Coordinating Centre for this study will be BC Cancer-Prince George under leadership of Dr. Robert Olson as Study Principal Investigator. Dr. Olson and the Coordinating Centre will be

responsible for trial activities at all participating sites, including international sites. The Coordinating Centre will be responsible for randomization of participants using a randomization module in the REDCap Electronic Data Capture (EDC) system, which will be used for trial data collection. In conjunction with trial statistician and Site Principal Investigators, the Coordinating Centre will be responsible for storing and analyzing trial data. Designated Site Principal Investigators will be responsible for reviewing eligibility of participants at their centre. In addition to providing credentials, evidence of regulatory training, and evidence of IRB/REB approval, all sites will receive protocol training and data entry training prior to site initiations.

13. References

1. Hellman, Samuel, and Ralph R. Weichselbaum. "Oligometastases." Journal of Clinical Oncology 13.1 (1995): 8-10.
2. Hong JC, Ayala-Peacock DN, Lee J, et al: Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: A multi-institutional pooled analysis. PLoS ONE 13:e0195149, 2018
3. Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H, Putnam Jr JB. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The Journal of thoracic and cardiovascular surgery. 1997 Jan 1;113(1):37-49.
4. Primrose, John, Tom Treasure, and Francesca Fiorentino. "Lung metastasectomy in colorectal cancer: is this surgery effective in prolonging life?." Respirology 15.5 (2010): 742-746.
5. Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, et al. The oligometastatic state—separating truth from wishful thinking. Nat Rev Clin Oncol. 2014 Sep;11(9):549
6. Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. Lung cancer. 2013 Nov 1;82(2):197-203.
7. Ruers T, Van Coevorden F, Punt CJ, et al: Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst 109, 2017
8. Ruers T, Punt C, Van Coevorden F, et al: Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Annals of Oncology 23:2619-2626, 2012
9. Palma DA, Haasbeek CJ, Rodrigues GB, Dahele M, Lock M, Yaremko B, Olson R, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (SABR-COMET): study protocol for a randomized phase II trial. BMC cancer. 2012 Dec;12(1):305.
10. Palma D, Olson R, Harrow S, Gaede S, Louie A, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard-of-care palliative treatment in patients with oligometastatic cancer (SABR-COMET): a randomized, phase II, open-label trial. Lancet. 2019; 393(10185;2051-
11. Palma, David A., Alexander V. Louie, and George B. Rodrigues. "New strategies in stereotactic radiotherapy for oligometastases." Clinical Cancer Research 21.23 (2015): 5198-5204.
12. Correa RJ, Salama JK, Milano MT, et al: Stereotactic Body Radiotherapy for Oligometastasis: Opportunities for Biology to Guide Clinical Management. Cancer J 22:247-56, 2016
13. Lussier YA, Khodarev NN, Regan K, et al: Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. PLoS One 7:e50141, 2012

14. Lussier YA, Xing HR, Salama JK, et al: MicroRNA expression characterizes oligometastasis(es). PLoS One 6:e28650, 2011
15. Uppal A, Wightman SC, Mallon S, et al: 14q32-encoded microRNAs mediate an oligometastatic phenotype. Oncotarget 6:3540-52, 2015
16. Lambert AW, Pattabiraman DR, Weinberg RA: Emerging Biological Principles of Metastasis. Cell 168:670-691, 2017
17. Cox BW, Spratt DE, Lovelock M, et al: International spine radiosurgery consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 83:597, 2012
18. Redmond KJ, Robertson S, Lo SS, Soltys SG, Ryu S, McNutt T, et al. Consensus contouring guidelines for postoperative stereotactic body radiation therapy for metastatic solid tumor malignancies to the spine. Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):64-74
19. Hong JC, Ayala-Peacock DN, Lee J, et al: Classification for long-term survival in oligometastatic patients treated with ablative radiotherapy: A multi-institutional pooled analysis. PLoS One 13:e0195149, 2018
20. Food and Drug Administration. E9: statistical principles for clinical trials. Federal Register. 1998 Sep 16;63(179):49583-98.
21. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec 1;20(10):1727-36.
22. Devlin NJ, Krabbe PFM: The Development of New Research Methods for the Valuation of EQ-5D-5L. Eur J Health Econ. 2013 Jul;14(S1–S3):1–3
23. Rabin R, Charro FD. EQ-SD: a measure of health status from the EuroQol Group. Ann Med. 2001 Jan 1;33(5):337-43.
24. Pickard AS, Wilke CT, Lin HW, Lloyd A. Health utilities using the EQ-5D in studies of cancer. Pharmacoeconomics. 2007 May 1;25(5):365-84.
25. National Institute for Clinical Excellence. Guide to the methods of technology appraisal. http://www. nice.org.Uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal. jsp. 2008.
26. National Cancer Institute, 2017. Common terminology criteria for adverse events (CTCAE) v5.0.
27. Alix-Panabières C, Pantel K. Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy. Cancer Discov. 2016 May 1;6(5):479-91.
28. De Goeje PL, Smit EF, Waasdorp C, Schram MT, Kaijen-Lambers ME, Bezemer K, et al. Stereotactic Ablative Radiotherapy Induces Peripheral T-Cell Activation in Patients with Early-Stage Lung Cancer. Am J Respir Crit Care Med. 2017 Nov 1;196(9):1224-7.
29. Merker JD, Oxnard GR, Compton C, et al: Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol 36:1631-1641, 2018
30. Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, Le Quesne J, Moore DA, Veeriah S, Rosenthal R, Marafioti T. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature. 2017 May;545(7655):446

31. Lambert AW, Pattabiraman DR, Weinberg RA: Emerging Biological Principles of Metastasis. Cell 168:670-691, 2017
32. Turajlic S, Xu H, Litchfield K, Rowan A, Chambers T, Lopez JI, Nicol D, O'Brien T, Larkin J, Horswell S, Stares M. Tracking cancer evolution reveals constrained routes to metastases: TRACERx Renal. Cell. 2018 Apr 19;173(3):581-94.
33. Jamal-Hanjani M, Wilson GA, McGranahan N, et al: Tracking the Evolution of Non-Small-Cell Lung Cancer. N Engl J Med 376:2109-2121, 2017
34. American Cancer Society. (2015, June 30). A Guide to Radiation Therapy.
35. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar 1;11(3):570-9.
36. De Oliveira C, Pataky R, Bremner KE, Rangrej J, Chan KK, Cheung WY, Hoch JS, Peacock S, Krahn MD. Estimating the cost of cancer care in British Columbia and Ontario: a Canadian inter-provincial comparison. Healthcare Policy. 2017 Feb;12(3):95.23. National Institute for Clinical Excellence.
37. Lee KM, McCarron CE, Bryan S. Guidelines for Economic Evaluation of Health Technologies: Canada. Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa. 2006.
38. Statistics Canada (Internet). Table 18-10-0004-13 Consumer Price Index by product group, monthly, percentage change, not seasonally adjusted, Canada, provinces, Whitehorse, Yellowknife and Iqaluit; 2019 Aug 08 (cited 2019 Aug 08). Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/cpis01a-eng.htm
39. Davis AA, Pierga JY, Dirix LY, Michiels S, Rademaker A, Reuben JM, et al. The impact of circulating tumor cells (CTCs) detection in metastatic breast cancer (MBC): Implications of "indolent" stage IV disease (Stage IVindolent). J Clin Oncol. 2018 May 20;36(15):1019-1019
40. Lopez-Soto A, Gonzalez S, Smyth MJ, Galluzzi L. Control of metastasis by NK cells. Cancer cell. 2017 Aug 14;32(2):135-54.
41. Demaria S, Coleman CN, Formenti SC. Radiotherapy: changing the game in immunotherapy. Trends Cancer. 2016 Jun 1;2(6):286-94.41.
42. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nature Reviews Cancer. 2018 May;18(5):313.

Appendix:

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 4 SABR ORGAN-AT-RISK (OAR) CONSTRAINTS

OAR	SABR ORGAN-AT-RISK (OAR) CONSTRAINTS				
	Dmax to ≤=0.035cc for all OARs.				
	Fractions				
	2	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.				
	Fractions				
	2	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
Renal 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

OAR	SABR ORGAN-AT-RISK (OAR) CONSTRAINTS				
	Dmax to ≤=0.035cc for all OARs.				
	Fractions				
	2	3	4	5	8
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).

[1] Benedict SH et al., AAPM TG101, Med.Phys 37(9), 2010 (NB: max pt = 0.035cc)
[2] Palma et al., SABR-COMET Trial, Palma et al, v.1.9, Apr 2015
[3] RTOG 0915, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915.
[4] Forquer JA et al., Radiother Onc, 93:408-413, 2009
[5] Karlsson K et al., IJROBP, 87(3): 590-595, 2013
[6] Dunlap NE et al., IJROBP 76(3): 796-801, 2010
[7] Andolino DL et al., IJROBP 80(3): 692-697, 2011
[8] Baker R, IJROBP, 85(1):190-195, 2013
[9] Matsuo Yet al., IJROBP, 83(4): e545-549, 2012.
[10] Bongers EM et al., Radiother Onc, 109: 95-99, 2013 (VU EMC TO 2013)
[11] Sahgal A et al., IJROBP, 82(1):107-116, 2012
[12] Sahgal et al., NCIC CTG Protocol #SC.24. Feb 2, 2017
[13] Sahgal A et al., IJROBP, 85(2):341-7, 2013 (Table 5; using 5% risk as per Sahgal ; personal communication Feb 2017)
[14] BCCA liver protocol 2011
[15] Velec M, et al, IJROBP (2017), doi: 10.1016/j.ijrobp.2017.01.221
[16] Grimm, et al, JACMP (2011), 12(2) 267
[17] Hiniker, et al., Sem Radiat Oncol 26(2), 97-104, 2016. DOI: (10.1016/j.semradonc.2015.11.008)
[18] Rashid, et al., Sem Radiati Oncol 26(2) 105-111, 2016. DOI: (10.1016/j.semradonc.2015.11.004)
[19] Kimsey et al., Sem Radiat Oncol 26(2), 129-134, 2016. DOI: (10.1016/j.semradonc.2015.11.003)
[20] Xue et al, Sem Radiat Oncol 26(2), 135-139, 2016. DOI: (10.1016/j.semradonc.2015.11.001)

[21]Nuyttens et al., Sem Radiat Oncol 26(2), 120-128, 2016. DOI: (10.1016/j.semradonc.2015.11.006)
[22]Goldsmith et al., Sem Radiat Oncol 26(2), 149-156, 2016. DOI: (10.1016/j.semradonc.2015.12.002)
[23] LaCouture et al., Sem Radiat Oncol 26(2), 157-164, 2016. DOI: (10.1016/j.semradonc.2015.11.009)

Constraints for Dose Spillage and Conformality

The R100 (ratio of size of prescription isodose volume to size of PTV) should be less than 1.2. Exceptions are allowed for small PTVs. The R50 (ratio of size of 50% prescription isodose volume to size of PTV) should be as low as possible and conform to the table below. Values for the maximum dose 2 cm or more away from the PTV (D2cm) is below.

	R50%		D2cm[%]	
	Per Protocol	Acceptable Variation	Per Protocol	Acceptable Variation
1.8	<5.9	<7.5	<50.0	<57.0
3.8	<5.5	<6.5	<50.0	<57.0
7.4	<5.1	<6.0	<50.0	<58.0
13.2	<4.7	<5.8	<50.0	<58.0
22.0	<4.5	<5.5	<54.0	<63.0
34.0	<4.3	<5.3	<58.0	<68.0
50.0	<4.0	<5.0	<62.0	<77.0
70.0	<3.5	<4.8	<66.0	<86.0
95.0	<3.3	<4.4	<70.0	<89.0
126.0	<3.1	<4.0	<73.0	<91.0
163.0	<2.9	<3.7	<77.0	<94.0

Source: NRG LU002 trial protocol

PROTOCOL SIGNATURE PAGE

Protocol Title: Phase III Randomized Controlled Trial and Economic Evaluation of Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic (1-3 metastases) cancer: SABR-COMET-3

Protocol Version/ Date: v13.0; 15 May 2024

Sponsor-Investigator Name: Dr. Robert Olson

Site: _____

Declaration of Investigator

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: _____