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STUDY PROTOCOL

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A randomized phase III trial of stereotactic ablative radiotherapy for patients with up to 10 oligometastases and a synchronous primary tumor (SABR-SYNC): study protocol

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Abstract

Background Emerging randomized data, mostly from phase II trials, have suggested that patients with oligometastatic cancers may benefit from ablative treatments such as stereotactic ablative radiotherapy (SABR). However, phase III data testing this paradigm are lacking, and many studies have examined SABR in the setting of metachronous oligometastatic disease. The goal of the SABR-SYNC trial is to assess the effect of SABR in patients with oligometastatic cancers and a synchronous primary tumor.

Methods One hundred and eighty patients will be randomized in a 1:2 ratio between standard of care (SOC) palliative-intent treatments vs. SOC + ablative therapy (SABR preferred) to all sites of known disease. Randomization will be stratified based on histology and number of metastases at enrollment. SABR may be delivered in 1-, 3- and 5-fraction regimens, with recommended doses of 20 Gy, 30 Gy, and 35 Gy, respectively. Non-SABR local modalities (e.g. surgery, thermal ablation, conventional radiation) may be used for treatment of the primary or metastases at the discretion of the treating physicians, if those modalities are clinically preferred. The primary endpoint is overall survival, and secondary endpoints include progression-free survival, time to development of new metastatic lesions, time to initiation of next systemic therapy, quality of life, and toxicity. Translational endpoints include assessment of circulating tumor DNA and immunological predictors of outcomes.

Discussion SABR-SYNC will provide phase III data to assess the impact of SABR on overall survival in a population of patients with synchronous oligometastases. The translational component will attempt to identify novel prognostic and predictive biomarkers to aid in clinical decision making.

Trial registration Clinicaltrials.gov NCT05717166 (registration date: Feb. 8, 2023).

Keywords Oligometastases, Synchronous, Stereotactic ablative radiotherapy, Quality of life

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Introduction

The oligometastatic state, first defined in 1995 [1] represents a scenario where a cancer has metastasized to only a limited number of locations. Over the past decade, several randomized trials have indicated that in patients with oligometastases, treatment with ablative therapies such as surgery or stereotactic ablative radiotherapy (SABR) can improve patient outcomes, including overall survival (OS) and progression-free survival (PFS) (Table 1).

Although most studies using ablative therapies have been limited to patients with 1–3 or 1–5 metastases, there is a growing number of trials investigating the role of SABR in patients with more widely metastatic disease. The SABR-COMET-10 phase III trial, which completed accrual in late 2023, enrolled patients with a controlled primary solid tumor of any histology, with 4–10 metastatic lesions, and randomized them in a 1:2 ratio between standard palliative treatments vs. SABR to all lesions [2]. In the population of patients with more than 10 metastases, the ARREST phase I trial tested the safety of SABR using a 3 + 3 design [3]. ARREST completed accrual in 2023, and led to the recently-activated phase II/III ARREST2 trial (NCT05508464).

However, despite this rapid increase in reported trials for patients with oligometastases, there remains a lack of data on the optimal approaches in patients with oligometastases and synchronous primary cancers. All of the COMET-series trials (the original SABR-COMET trial, along with SABR-COMET-3 for 1–3 metastases [4] and SABR-COMET-10 for 4–10 metastases) required patients to have a controlled primary tumor, since such patients generally have the best prognosis among patients with oligometastases [5]. Although the presence of synchronous disease may portend a worse prognosis overall, such patients may still benefit from SABR: several of the phase II trials in Table 1 allowed patients to be included with synchronous primary tumors [6–9]. However, phase III data in this population are lacking.

In summary, it is unclear if patients with synchronous oligometastases benefit from SABR, in terms of improved OS, PFS, or quality of life (QOL). The purpose of this randomized trial is to assess the impact of SABR on outcomes in patients with an untreated primary tumor and 1–10 oligometastatic lesions.

Objectives

To assess the impact of the addition of SABR to standard of care treatment, compared to standard of care treatment alone, on OS, oncologic outcomes, and QOL in patients with an intact primary tumor and 1–10 metastatic lesions.

Primary endpoint

- OS
    - Defined as time from randomization to death from any cause, or date of last follow-up, whichever occurs first.

Table 1 Selected randomized trials of ablative therapies for patients with oligometastases

Histology	Trial Name / Author	Intervention	Benefit Demonstrated
NSCLC	Gomez [6]	RT or surgery	OS, PFS
	Iyengar [7]	SABR	PFS
	SINDAS / Wang [10]	SABR	OS, PFS
	Peng [11]	SABR	OS, PFS
Prostate	STOMP / Ost [8]	RT or surgery	ADT-free survival
	ORIOLE / Phillips [9]	SABR	PFS
	EXTEND / Tang [12]	RT / SABR	PFS
	ARTO / Francolini [13]	SABR	PFS
Colorectal	EORTC 40004 / Ruers [14]	RFA (liver)	OS, PFS
	PulMiCC / Treasure [15]	Surgery (lung)	None
Pancreas	EXTEND / Ludmir [16]	RT / SABR	PFS
Breast	BR002 / Chmura [17]	SABR or surgery	None
Esophageal	ESO-Shanghai-13 / Liu [18]	RT, surgery, TA	OS, PFS
Multiple	SABR-COMET / Palma [19]	SABR	OS, PFS
	CORE / Khoo [20]	SABR	PFS

NSCLC non-small cell lung cancer, *RT* radiotherapy, *SABR* stereotactic ablative radiotherapy, *RFA* radiofrequency ablation, *TA* thermal ablation, *OS* overall survival, *PFS* progression-free survival, *ADT* androgen deprivation therapy

Secondary endpoints

- PFS
  - Defined as time from randomization to death from any cause, progression of disease, or date of last follow-up, whichever occurs first.
- QOL
  - Assessed with the Functional Assessment of Cancer Therapy: General (FACT-G) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L).
- Toxicity
  - Assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 5 for each organ treated (e.g. liver, lung, bone).
- Time to next systemic therapy
  - Defined as the time from randomization until commencement of any systemic anti-cancer therapy, or date of last follow-up, whichever occurs first.
- Receipt of additional radiation during follow-up
  - Will be collected for SABR (as a binary endpoint; yes/no), and non-SABR (yes/no).

Translational endpoints

- Assessment of cell-free DNA, and tumor DNA as prognostic and predictive biomarkers of survival, and for early detection of progression.
- Assessment of immunological predictors of response and long-term survival.

Study design

This study is a phase III multi-institutional 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 (Fig. 1).

Patients will be stratified by two of the strongest prognostic factors, based on a large multi-institutional analysis [21]: histology (Group 1: hormone-sensitive prostate cancer, breast, or renal; Group 2: all others), and number of metastases (Group 1: 1–3; Group 2: 4–10).

Patient selection

Inclusion criteria

- Age 18 years or older
- Willing to provide informed consent
- Karnofsky performance status > 60
- Life expectancy > 6 months
- Histologically confirmed malignancy with metastatic disease detected on imaging. Biopsy of metastasis is preferred, but not required.
- Total number of metastases 1–10 at the time of enrollment, with a primary tumor also present.
- Restaging completed within 12 weeks prior to randomization (see Investigations Section).
- For patients receiving thoracic radiotherapy, the enrolling physician must confirm there are no computed tomography (CT) changes suggestive of fibrotic interstitial lung disease (ILD) (i.e. reticular changes, traction bronchiectasis, or honeycombing) reported on any prior CT scans. If any are present, the patient must be assessed by a respirologist to rule out ILD prior to enrollment.

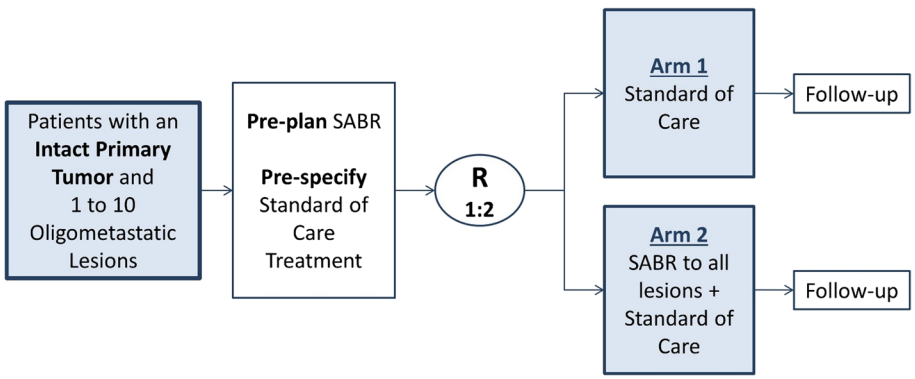

Fig. 1 Study schema

Exclusion criteria

- Serious medical comorbidities precluding radiotherapy. These include ILD in patients requiring thoracic radiation, Crohn's disease in patients where the gastrointestinal (GI) tract will receive radiotherapy, or ulcerative colitis where the bowel will receive radiotherapy, and connective tissue disorders such as lupus or scleroderma.
- For patients with liver metastases, moderate/severe liver dysfunction (Child Pugh B or C).
- 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 in Appendix 1. All such cases must be discussed with a member of the study steering committee.
- Malignant pleural effusion
- Inability to treat all sites of disease
- Brain metastasis > 3 cm in size or a total volume of brain metastases greater than 30 cc.
- Metastasis in the brainstem
- Clinical or radiologic evidence of spinal cord compression
- Metastatic disease that invades any of the following: GI tract (including esophagus, stomach, small or large bowel), or skin
- Pregnant or lactating women

Pre-treatment evaluation

Investigations

- History and Physical Examination
    - Including prior cancer therapies and concomitant cancer-related medications.
- Restaging within 12 weeks prior to randomization:
    - Brain: CT or magnetic resonance imaging (MRI) for tumor sites with propensity for brain metastasis. All patients with brain metastases (at enrollment or previously treated) require an MRI.
    - Body: 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT imaging is recommended, except for tumors where FDG uptake is not expected (e.g. prostate, renal cell carcinoma). Prostate-specific membrane antigen (PSMA)-PET or choline-PET is recommended for prostate cancer. In situations where a PET scan is unavailable, or for tumors that do not take up radiotracer, CT chest/abdomen/pelvis is required with optional bone scan.
    - Spine: MRI required for patients with vertebral or paraspinal metastases. The MRI needs to image the area being treated and one vertebra above and below as a minimum, but does not need to be a whole spine MRI unless clinically indicated.
- For patients with liver metastases: liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], glutamyl transferase [GGT], alkaline phosphatase), albumin, bilirubin, and international normalized ratio (INR), and liver MRI is strongly recommended.
- Pregnancy test for women of child-bearing age.
- Completion of QOL questionnaires (FACT-G, EQ-5D-5L).

Defining the number of metastases

i) Counting metastases

Patients are eligible if there are 1–10 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. There is no limit to the number of metastases in each individual organ, as long as dose constraints can be met in the pre-plan.

ii) Previously treated metastases

Patients with prior metastases that have been treated with ablative therapies (e.g. SABR, surgery, radiofrequency ablation [RFA]) are eligible, as long as those metastases are controlled on imaging. If the metastasis is progressing, it must be treatable (see Dose/Fractionation for the Primary Tumor and Metastases Section for treatment options).

iii) Small or indeterminate lesions

When patients have small indeterminate nodules (e.g. a 3 mm lung nodule) it can be difficult to determine whether these are benign or whether they represent metastasis. This study will rely on the judgement of the enrolling investigator for final determination. The presence or absence of such indeterminate lesions will be noted on the study enrollment form.

If a lesion is too small to treat due to targeting issues (e.g. a 3 mm lung lesion not likely to be visible on cone beam

CT [CBCT]), the following approach is to be taken: if randomized to Arm 1, no intervention is needed, since such a lesion would not require palliative radiation. If randomized to Arm 2, the lesion is followed, and upon progression to a size that is treatable, it should be treated with SABR.

iv) Regressing lesions

If the primary tumor has regressed with systemic therapy and is no longer visible on imaging and physical examination, it is not required to be treated on Arm 2. If the lesion then progresses and is targetable later, it should generally be treated as long as other disease sites are controlled or controllable.

Brain metastases at presentation

If a patient presents with up to 5 brain metastases and ablation of those metastases (with surgery or radiation) is judged to be clinically required regardless of the treatment of extracranial metastases, it is permitted. Those treated metastases count within the total number of 10 lesions. The patient can then be enrolled as long as there is untreated extracranial disease. The patient would then be randomized to treatment of the extracranial disease or not.

Patients already receiving systemic therapy

If a patient is already receiving systemic therapy, they are still eligible for enrollment. For example, if a patient with 5 metastases has been on chemotherapy for 1 year and is planning to continue, they can still be randomized, and if allocated to the standard of care arm would continue to receive chemotherapy; on the experimental arm SABR would be delivered between cycles, possibly requiring a break in systemic therapy to comply with the timing of systemic therapy described in Systemic Therapy Section.

Registration, data collection and randomization procedure

i) Pre-specification of treatment approaches

Prior to randomization, the enrolling investigator will pre-specify the treatment(s) that would be delivered on each arm.

The investigator will specify:

- Intended systemic therapy (yes/no) on Arm 1 and Arm 2 (these should generally be the same, unless giving chemoradiation in Arm 2), including the type of systemic therapy (cytotoxic, targeted, hormonal, immunotherapy, or other).
- Intended palliative treatment to any lesions (yes/no) if randomized to Arm 1, and the type of treatment (SABR, fractionated radiation, surgery; see Standard Arm (Arm 1) Section for allowable treatments on Arm 1).
- Intended treatment of the primary tumor and each metastasis if randomized to Arm 2 (SABR, fractionated radiation, chemoradiation, surgery, other).

Treatment plan

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. 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 in this arm should not receive ablative treatments or radical-intent treatments (e.g. surgery), unless there is a clearly known clinical benefit (e.g. stereotactic radiation to a new brain metastasis when other disease is controlled on systemic therapy, or treatment of the prostate in the setting of low-burden disease elsewhere). Even when some lesions are treated in this manner, patients should not receive treatment to all lesions in the standard arm. If the investigator judges that all lesions would be treated with ablative therapies on Arm 1 as part of standard of care, the patient should not be randomized.

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 Systemic Therapy Section for the timing of systemic therapy.

Experimental arm (Arm 2)

Arm 2 consists of treatment to the primary tumor and metastases, with SABR preferred, but other options all allowable (e.g. surgery, RFA, fractionated radiation, chemoradiation) if those are deemed to be preferable by the treating oncologists (see Dose/Fractionation for the Primary Tumor and Metastases Section).

Pre-planning procedure

It is recommended (but not required) to complete a radiation pre-plan before enrollment. In cases that are very clearly plannable (e.g. a small lung primary tumor and two bone metastases, or a primary tumor to be resected on Arm 2 with a single metastasis to be treated with SABR), the pre-plan can be omitted.

If a patient undergoes pre-planning but cannot be randomized due to failure to generate an acceptable plan, the baseline information of such patients will be captured (i.e. the Eligibility Checklist and Baseline Form), but they will not be followed for outcomes. If there are lesions that will not be treated with radiation (e.g. they will be resected), then those are to be ignored on the pre-plan.

Institutions may use diagnostic images rather than radiation planning images for pre-planning. To minimize

the risk of progression or development of new lesions between the diagnostic images and the eventual CT simulation, the diagnostic images must be less than 4 weeks old by the time of randomization (i.e. after the pre-plan is done). If randomized to Arm 2, CT simulation and planning must occur such that radiation starts within 2 weeks of randomization.

Institutions may send treatment plans to the coordinating centre if the sites wish to have their plans reviewed (this is not mandatory) or if requested by the coordinating centre.

Dose/fractionation for the primary tumor and metastases

Treatment of the primary tumor The primary tumor and any involved regional nodes may be treated with SABR (using the dose fractionations in Treatment of Metastases Section) or with other local modalities (surgery, fractionated radiation [e.g. 40 Gy in 15 fractions], or chemoradiation) at the discretion of the treating team and/or the local multidisciplinary tumor board. Because of the convenience in using SABR for all lesions, non-SABR modalities should only be used if they are likely to provide a benefit over SABR (e.g. better local control with chemoradiation for stage III intrathoracic lung cancer, or with surgery for a colorectal primary).

If SABR is being used, most primary tumors will be treatable with the fractionations in Treatment of Metastases Section. However, tumors in the esophagus, stomach, small intestine or colon should be treated with either fractionated radiation or a lower SABR dose (e.g. 25 Gy in 5 fractions) to minimize the risk of perforation.

Treatment of metastases Each lesion may be treated with 1, 3, or 5 fractions, depending on the local practice of the enrolling institution and treating physician. All doses are prescribed to the periphery of the planning target volume (PTV). Acceptable fractionations are listed in Table 2.

Note for vertebral metastases: for centres that standardly treat vertebral metastases with 24 Gy in 2 fractions and would prefer to use that fractionation, this is allowable. Organ at risk (OAR) dose constraints should be the same as was used for the SC-24 trial and can be found in the supplemental appendix of the SC-24 trial publication [22]. However, as noted in Volume Definition (Arm 2) section, it is recommended that the spine target volumes consist of the lesion only plus an additional margin, rather than the whole vertebral body, to avoid large volumes of bone marrow irradiation.

Table 2 Radiation fractionation options for metastatic lesions

Number of Fractions[a]	Preferred Dose	Acceptable Doses	Major Deviation
1	20 Gy	16–24 Gy	< 16 Gy or > 24 Gy
3	30 Gy	24–33 Gy	< 24 Gy or > 33 Gy
5	35 Gy	25–40 Gy	< 25 Gy or > 40 Gy

[a] Three-fraction regimens will deliver a fraction every second day, and five-fraction regimens will be delivered daily

Non-SABR treatments may be used for metastases (e.g. resection or RFA) if they are thought to provide an advantage in the treatment of a specific metastases (e.g. resecting a lesion to collect tissue for molecular biomarkers, resecting a lesion in a location not easily amenable to SABR, or resecting a lesion that was previously radiated but progressing).

Immobilization

Treatment will be setup using reproducible positioning and verified using an online 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 institutions do not use immobilization devices and have demonstrated high degrees of accuracy; this is acceptable in this study.

Imaging/localization/registration

All patients in Arm 2 will undergo planning CT simulation. Axial CT images will be obtained throughout the region of interest. For institutions using stereotactic radiosurgery platforms, real-time tumor tracking and orthogonal imaging systems are permitted.

Patients may be treated with MRI-guided delivery if deemed appropriate by the treating oncologist, and may use daily plan adaptation as has been described previously.[4–7] 4D-CT Procedures Section will not apply to these patients.

4D-CT procedures

Four-dimensional (4D) CT will be used for tumors in the lungs, liver, or adrenals. For patients undergoing 4D-CT, physics will review the 4D-CT images and will perform standard quality assurance (QA) procedures indicated on the 4D-CT template designed specifically for SABR. Motion measurements in all 3 directions are required and each institution must have a strategy for motion management.

Volume definitions (Arm 2)

For SABR, the gross tumor volume (GTV) will be defined as the visible tumor 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 vertebral body lesions, although current guidelines consider the entire vertebral body as the CTV, that is not preferred in this trial due to the risk of large cumulative amounts of bone marrow being irradiated. It is preferred that vertebral PTVs consist of the GTV (as defined on CT and MRI) with a small margin for motion, and NOT include the whole uninvolved vertebral body, unless the number of spinal lesions/levels being treated is small (e.g. 1–3). A PTV margin of 2–5 mm will be added depending on site of disease, immobilization, and institutional setup accuracy: 2 mm margins should be used for spinal stereotactic treatments, 0–2 mm for brain tumors, and 5 mm for other sites.

For fractionated radiotherapy, target volumes are the same as for SABR, except that a CTV of up to 5 mm is allowed, but not required.

Targets should be named based on the organ involved, and numbered from cranially to caudally for each organ. For example, in a patient with 1 brain and 3 lung lesions, there would be: GTV_brain_1, GTV_lung_1, GTV_lung_2, and GTV_lung_3, and corresponding PTV_brain_1, PTV_lung_1, PTV_lung_2, and PTV_lung_3, representing the lesions from superior to inferior. In order to keep track of which lesions are being treated on each day, we strongly recommend use of a lesion tracking sheet, to specify which isocentres are being treated on which date; this sheet is available from the Principal Investigator upon request.

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.

OAR doses

OAR doses are listed in Appendix 1 [23]. OAR doses may not be exceeded. In cases where the PTV coverage cannot be achieved without exceeding OAR doses, the PTV coverage is to be compromised. All OARs within 5 cm of the PTV must be contoured. This can 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 3-dimensional (3D)-conformal radiotherapy or intensity-modulated) or rotational therapy (volumetric modulated arc therapy [VMAT], or tomotherapy). Priority will be placed on generating clinically acceptable plans while minimizing complexity, planning time, and treatment time.

Dose constraints may not be exceeded**.** If a dose constraint cannot be achieved due to overlap of the target with an OAR, the dose can be reduced, the number of fractions can be increased, or the target coverage compromised in order to meet the constraint. The decision as to whether to reduce the dose to the whole target, or part of the target (i.e. by compromising the PTV coverage), is left to the discretion of the treating physician. In cases where the target coverage 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). For vertebral tumors, note that the spinal cord constraints apply to the PRV (see 4D-CT Procedures Section).

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 the prescription dose, and 99% of the PTV should be covered by 90% of the prescription dose.

Doses must be corrected for tissue inhomogeneities. 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 volume.

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 the primary and each metastasis is at the discretion of individual physicians, but in general should begin with the brain, due to risks associated with progression.

Treatment should start within two weeks of randomization, and treatment of all lesions (including the primary and metastases) should be delivered in as short a time-frame as feasible, although there is no strict requirement for a maximum treatment period.

Quality assurance (Arm 2)

The following requirements must be completed for each patient:

- Prior to treatment, plans for each patient must be peer-reviewed, either by discussion at QA rounds or by another individual radiation oncologist.
- All radiotherapy plans must meet target dose levels for OARs (Appendix 1). Prior to plan approval, the dose to each OAR 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.

Systemic therapy

Patients treated with prior systemic therapy are eligible for this study. Cytotoxic agents must be held commencing 2 weeks prior to radiation and lasting until 1 week after the last fraction. Molecularly targeted agents must be held for at least 48 h before the first fraction until 48 h after the last fraction. Immunotherapy and hormone therapy are exempted from these requirements and are allowed during treatment but patients who are on hormone therapy with cyclin-dependent kinase (CDK) 4/6 inhibitors must stop the latter during this three-week period. Use of chemotherapy schemes containing potent enhancers of radiation damage (e.g. gemcitabine, doxorubicin) and vascular endothelial growth factor inhibitors (e.g. bevacizumab) are discouraged within the first month after radiation.

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).

Patients in Arm 2 who develop new, untreated metastatic deposits should be considered for SABR at those sites, as appropriate, 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 radiotherapy can be delivered if indicated. Patients in Arm 2 who develop progression at lesion previously treated with SABR may be considered for palliative radiation or repeat SABR if safe and dose constraints can be met.

QA for participating institutions

Prior to opening the study, each participating institution will be required to send to one of the Principal Investigators 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 Principal Investigators will provide pertinent CT datasets. Alternatively, a pre-plan for a patient enrolled on this trial may be used for credentialing. Each participating institution can choose which tumor sites will be treated at their individual institution (i.e. some institutions 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.

Adverse events

Adverse events will be scored using the CTCAE version 5 scale. Full definitions of adverse events, serious adverse events, and causality attribution have been previously published [2] and for brevity are not repeated here.

Subject discontinuation / withdrawal

Subjects may voluntarily discontinue participation in the study at any time. If a subject is removed from the study, the clinical and laboratory evaluations that would have been performed at the end of the study should be obtained. If a subject is removed because of an adverse event, they should remain under medical observation as long as deemed appropriate by the treating physician.

Follow-up evaluation and assessment of efficacy

This trial is employing a pragmatic study design, to minimize burden on patients and participating institutions. The visits and procedures in Assessment Schedule and Assessment of Efficacy Section are required for study data collection, but patients should be followed as per standard of care frequency for clinical and imaging visits at their treating institution (e.g. every 3–6 months). After progression of disease, further imaging is at the discretion of the treating oncologist, but patients should still be followed for survival, toxicity, QOL, and other endpoints.

Assessment schedule

Required follow-up interactions (in-person preferred but telephone/video allowed), measured from time since the end of treatment are shown in Table 3. Toxicity and QOL outcomes are only mandated to be collected for the first 2 years, with only vital status collected thereafter. However, new grade 2–5 toxicities that occur beyond 2 years should still be reported in REDCap if it is determined that such a toxicity has occurred.

For patients who are not seen in person, QOL and toxicity scoring may be completed by mail, email or by telephone.

Assessment of efficacy

- OS
    - Defined as time from randomization to death from any cause, or date of last follow-up, whichever occurs first.
- PFS
    - Defined as time from randomization to death from any cause, progression of disease, or date of last follow-up, whichever occurs first.

Table 3 Follow-up schema

	Randomization	Last week of treatment	6 weeks	3, 6, 12, 18, 24 months	36, 48, 60 months
Clinic visit, including documentation of initiation of new cancer treatments	X[a]	X	X	X	X[b]
Imaging	X[c]			X[d]	X[d]
Toxicity scoring (CTCAE version 5)		X	X	X	X[e]
QOL scoring (FACT-G and EQ-5D-5L)	X			X	

CTCAE Common Terminology Criteria for Adverse Events, *FACT-G* Functional Assessment of Cancer Therapy, General, *EQ-5D-5L* EuroQol 5-Dimension 5-Level

[a] Including medical history and physical examination

[b] Vital status update and initiation of new cancer related treatment only

[c] Imaging to be completed within 12 weeks of randomization, per Pre-Treatment Evaluation Section

[d] Imaging as per site standard of care, and after progression at discretion of treating oncologist

[e] new grade 2–5 toxicities if related to treatment

- This trial will not collect Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 measurements centrally, and progression will be assessed by the local oncologist. Progression is defined as a 20% increase in the sum of measurements of all lesions present at baseline (and this increase must be at least 5 mm) OR development of new lesions. If there are equivocal findings, such as changes around treated lesions that could be progression or radiation changes, or new lesions that could be metastases or inflammatory, then this is to be coded as progression. However, if on subsequent scans these findings are deemed non-malignant (e.g. if the lesions regress without systemic therapy), then this is revised to reflect no progression, consistent with RECIST 1.1 guidelines.

- QOL
  - Assessed with FACT-G and EQ-5D-5L.
- Toxicity
  - Assessed by the CTCAE version 5 for each organ treated (e.g. liver, lung, bone).
- Time to initiation of systemic therapy
  - Defined as the time from randomization to initiation of systemic therapy. Patients who are continuing a previous systemic therapy during radiotherapy (e.g. hormones) or have a brief pause to allow for radiation, will have this time recorded as zero.
- Receipt of additional radiation during follow-up
  - Will be collected for SABR (as a binary endpoint; yes/no), and non-SABR (yes/no).

Statistical considerations

Randomization

The study will employ a 1:2 randomization between Arm 1: Arm 2, based on the stratification factors described in Objectives Section. Patients will be randomized in permuted blocks, with the size of the blocks known only to the statistician until completion of the study.

Sample Size Calculation

We hypothesize that the median OS will be 12 months in Arm 1 and 20 months in Arm 2. In order to detect this difference, with an alpha of 0.05, 80% power, 2-sided testing and a 5% dropout rate**,** 180 patients will be required. The study projects accrual over 60 months with 12 months of additional follow-up.

Analysis plan

Patients will be analyzed in the groups to which they are assigned (intention-to-treat). OS and PFS will be calculated using the Kaplan–Meier method with differences compared using the stratified log-rank test. In addition to the intention-to-treat analysis for the primary endpoint, a per-protocol analysis will be done, analyzing patients as per the treatment actually received, with adjustment for crossover from Arm 1 to Arm 2 done using inverse probability censoring weighting or other techniques as appropriate. Pre-planned subgroup analyses will occur based on the stratification factors, including an analysis of outcomes by major histologic subtypes. Separate analyses of OS will also be done based on whether the primary tumor is treated with SABR vs. other approaches (e.g. surgery, chemoradiation, etc., see Dose/Fractionation section). A multivariable Cox proportional hazards regression analysis will be used to determine baseline factors

predictive of OS. QOL at 6 months will be measured using FACT-G and EQ-5D-5L scores, with differences between groups tested using the independent two-sample t-test, and linear mixed modeling (with time and treatment arm as fixed effects and patient number as a random effect) will be used to compare changes over time. Differences in rates of grade 2 or higher toxicity between groups will be tested using the chi-square test or Fisher's exact test, as appropriate.

Data Safety Monitoring Committee (DSMC)

The DSMC will meet annually after study initiation to review toxicity outcomes. If any grade 3–5 toxicity is reported, the DSMC will review the case notes to determine if such toxicity is related to treatment. If the DSMC deems that toxicity rates are excessive (>40% grade 3 toxicity, or >8% grade 5 toxicity), then the DSMC can, at its discretion, recommend cessation of the trial, dose adjustment, or exclusion of certain treatment sites and/or delivery techniques that are deemed as high-risk for complications.

Interim analysis

The DSMC will conduct one interim analysis once the 90th patient is accrued and followed for 6 months. For this interim analysis, the DSMC will be blinded to the identity of each treatment arm, but median OS data will be presented for each arm. 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 stratified log-rank test.

The trial will be stopped for futility if the hazard ratio for OS in Arm 2 vs. Arm 1 is >1.0 (i.e. a higher hazard rate for OS in the experimental arm using univariable Cox proportional hazards regression). Furthermore, if the median OS among all patients is substantially different than estimated in the sample size calculation, the DSMC or Principal Investigators can recommend increasing or decreasing the target accrual in order to maintain statistical power.

Dosimetric analysis

Anonymized radiation plans will be collected for a separate analysis of dosimetric data, including number of isocenters, beam arrangements, lesion coverage, and doses to normal structures. This is optional for the participating institutions.

Biomarker studies

Biomarker studies in this trial are optional, and each institution can indicate if they wish to opt in to the biomarker component of the study. Full details of the biomarker studies are provided in the Laboratory Manual (available on request to Principal Investigator).

In brief, the increased requirements, beyond standard of care testing, consist of drawing 2 tubes of blood at the following time periods (Fig. 2):

- Patients in Arm 1: at randomization, at 3-months post-randomization, and at disease progression or study completion (whichever is first).
- Patients in Arm 2: at randomization, 1–3 days after their first fraction of SABR, 1–4 weeks after completion of SABR (prior to systemic therapy), 3-months post-randomization, and at disease progression or study completion (whichever is first).

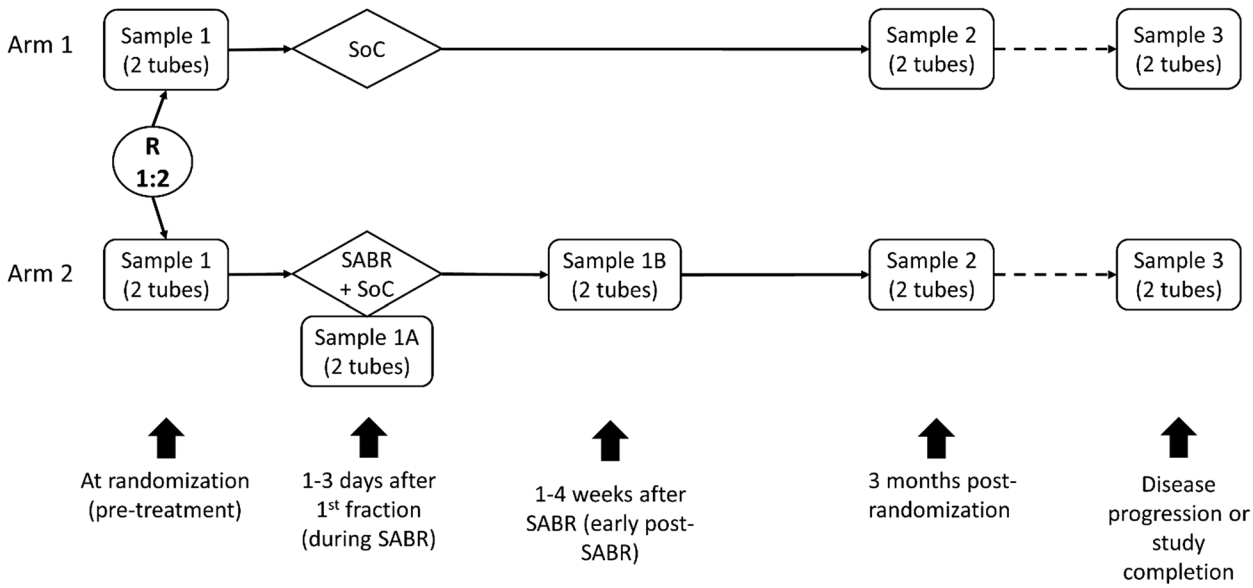

Fig. 2 Peripheral blood collection timeline. Samples will include vials of blood for circulating tumor (ct)DNA and peripheral blood mononuclear cell isolation. Abbreviations – SoC: standard of care; SABR: stereotactic ablative radiotherapy

In addition to the blood samples, this study will collect tissue samples from previous biopsies or resections of the primary tumor and metastases, where available. No additional biopsies will be needed for the purposes of the biomarker component of this trial beyond those collected as part of routine clinical care. If formalin-fixed paraffin-embedded (FFPE) tissue blocks are not available to be sent at the discretion of the local pathologist (e.g. insufficient tissue, or a need to keep all tissue for future purposes), the FFPE tissue blocks are not required and institutions can proceed by sending peripheral blood only.

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 Laboratory Manual. All shipping costs will be covered via the provision of pre-paid shipping labels, 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.

Discussion

Although several phase II randomized trials have shown potential benefits in treating oligometastatic disease with local therapies, phase III trials remain the gold-standard in evidence-based medicine. SABR-SYNC will test whether ablative therapies can impact important patient outcomes, including OS, PFS, toxicity, and QOL, in a population of patients with an untreated primary tumor and synchronous oligometastatic disease.

SABR-SYNC includes some pragmatic design considerations, intended to reduce the risk of study failure due to poor accrual [24]. First, SABR-SYNC includes patients with all solid tumor histologies, since a histology-specific restriction substantially reduces the population of patients eligible for enrollment. Although this trial stratifies patients by histology, and histology-specific subgroup analyses are planned, there may be important differences in biologic behaviour across histologies that may not be detected on subgroup analyses. Such differences were seen in the CURB trial testing SABR for oligoprogressive metastatic cancers, where a benefit was seen in patients with non-small cell lung cancer (NSCLC) but not in those with breast cancer [25], and these may be reflected in the negative findings of the BR002 trial, as shown in Table 1 [17]. Second, SABR is the recommended ablative treatment in SABR-SYNC, recognizing the large number of supporting phase II trials using SABR, and the ability to quickly deliver SABR to multiple sites in a short period of time. However, other local ablative therapies are permitted for both the primary and metastases, if the treating oncologists believe that those alternatives are more appropriate for a given clinical scenario, thus offering flexibility of management. Thirdly, rather than limiting this trial to patients with synchronous primary tumors and 1–3 metastases (analogous to SABR-COMET-3) or 4–10 metastases (analogous to SABR-COMET-10), this trial allows all patients with 1–10 metastases, with a pre-planned analysis to assess the impact of SABR in these two subgroups. These pragmatic decisions are intended to ensure timely accrual and stratification will ensure balance of these factors between the two treatment arms. However, target accruals for these important strata are not set, so the number of patients accrued within each of the subgroups may limit the conclusions that can be drawn from subgroup analyses of this trial. Such subanalyses may provide important treatment signals that can be explored in follow-up strata-specific trials.

Validated biomarkers are urgently needed to help guide treatment in patients with oligometastases [26, 27], particularly if they are able to detect occult micro-metastatic disease. The presence of occult micro-metastatic disease appears to be common in this patient population. In the original SABR-COMET trial, more than 80% of patients had a cancer progression event within 5-years after SABR, most of which were due to the development of distant metastases [19], which may have developed from occult metastases present at the time of original enrollment. Such biomarkers may better identify patients who have widespread occult micrometastatic disease who may benefit from a different treatment approach, either escalating the systemic therapy given around the time of SABR, or alternatively omitting SABR altogether to focus on systemic treatments. Conversely, patients without micrometastatic disease may not require systemic therapy, if local treatments are able to control visible lesions. Circulating biomarkers may also allow for early detection of recurrence, allowing for earlier identification and treatment of new metastases that arise after SABR. The biomarker analysis in this study will complement and add to the work on biomarkers included in other prospective trials.

In conclusion, SABR-SYNC will provide additional randomized evidence to understand the potentials benefit of SABR in the management of patients with oligometastatic disease. In particular SABR-SYNC will explore this option in patients with synchronous presentation with an untreated primary tumor, a population under represented in the current evidence base.

Appendix 1

Dose constraints

Dose constraints used herein are based on a systematic review of SABR trials,(24) and the previous SABR-COMET and SABR-COMET-10 trials. If any structure is not listed, the constraints may be taken from Gerhard et al. (24) or calculated using the linear quadratic formula from accepted QUANTEC doses, using an alpha–beta ratio of 2 for late effects.

In a situation where multiple fractionations are being used (e.g. some lesions with 3 fractions and some with 5), or if non-SABR radiotherapy is being used, then the equivalent dose in 2 Gy fractions (EQD2) conversions should be done using commercially available software and QUANTEC constraints should be used.

Note: For spinal lesions, a 24 Gy in 2 fraction regimen is allowed for centres that employ that as their standard approach. Please see Treatment of Metastases Section for details and dose constraints.

Table 4 Dose Constraints for Serial Structures. D0.03 cc = maximum dose in Gy allowable to the hottest 0.03 cc; other D values are used in the same way

Structure	Volume	1 Fraction	3 Fraction	5 Fraction
Optic Pathway	D0.03 cc	10	17.4	25
	D0.2 cc	8	15.3	23
Cochlea	D0.03 cc	9	17.1	22.5
Brainstem	D0.03 cc	15	23.1	31
	D0.5 cc	10	18	23
Spinal Cord	D0.03 cc	14	21.9	30
	D0.35 cc	10	18	23
Cauda Equina or Sacral Plexus	D0.03 cc	16	24	32
	D5cc	14	21.9	30
Esophagus	D0.03 cc	15.4	27	35
	D5cc	11.9	17.7	27.5
Brachial Plexus	D0.03 cc	17.5	24	30.5
	D3cc	14	20.4	27
Heart	D0.03 cc	22	30	38
	D15cc	16	24	32
Great Vessels	D0.03 cc	37	45	53
	D10cc	31	39	47
Trachea and large bronchi (mainstem, bronchus intermedius)	D0.03 cc	20.2	30	40
	D4cc	10.5	–-	–-
	D5cc	–-	25.8	32
Chest Wall or Rib	D0.03 cc	30	50	57
	D5cc	28	40	45
Skin	D0.03 cc	26	33	39.5
	D10cc	23	30	36.5
Stomach	D0.03 cc	12.4	30	32
	D10cc	11.2	16.5	26.5
Bile Ducts and Gallbladder	D0.03 cc	30	36	41
Duodenum	D0.03 cc	12.4	22.2	32
	D5cc	11.2	16.5	18
	D10cc	9	11.4	12.5
Jejunum or Ileum	D0.03 cc	15.4	25.2	35
	D30cc	12.5	17.4	20
Colon or Rectum	D0.03 cc	18.4	28.2	38
	D20cc	14.3	24	25
Ureter	D0.03 cc	35	40	45
Bladder	D0.03 cc	18.4	28.2	38
	D15cc	11.4	16.8	18.3
Penile Bulb	D3cc	16	25	30
Femoral Heads	D10cc	14	21.9	30

Table 5 Dose Constraints for Parallel Structures. Parallel structures require the use of a 'critical volume' (CV), also termed a 'complementary volume'. For example, for lung, the CV1500cc is listed as 7 Gy for 1-fraction treatments, meaning that there must be 1500 cc of lung receiving 7 Gy or less. This is read from the left-hand side of a dose-volume histogram (DVH). For further information on calculating the CV, with DVH examples, see *Application of Critical Volume-Dose Constraints for Stereotactic Body Radiation Therapy in NRG Radiation Therapy Trials* at https://www.redjournal.org/article/S0360-3016(17)30241-9/abstract. The VX refers to the percent of lung (minus GTVs) receiving X Gy or more

Structure	Volume	1 Fraction	3 Fraction	5 Fraction
Lung (combined right and left, subtract GTVs)	CV1500cc	7	10.5	12.5
	V8Gy(%)	37		
	V11Gy(%)		37	
	V13.5 Gy(%)			37
Liver	CV700cc	9.1	15	21
Kidney cortex (combined left and right)	CV200cc	8.4	16	17.5

For situations where multiple single fractions are delivered but on different days (e.g. 5 lung lesions, each treated with a single fraction over 5 days of total treatment time), the multiple-fraction dose constraints for parallel structures may be more appropriate than the single fraction dose constraints, in the judgement of the treating oncologist.

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 one of the tables below. Values for the maximum dose 2 cm or more away from the PTV (D2cm) is below. An attempt should be made to meet the RTOG dose constraints (Table 6 in Appendix 1), but if not feasible, the ROSEL/SABR-COMET dose constraints are acceptable (Table 7 in Appendix 1).

These constraints are recommended, not mandatory.

In some cases (e.g. two or more lesions in close proximity), these constraints cannot be met. Treatment may proceed as long as the constraints in Tables 4 and 5 in Appendix 1 are met.

Table 6 RTOG dose constraints

	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

Table 7 SABR-COMET/ROSEL dose constraints

Type B models (more advanced algorithms)								
$R_{100\%}$		$R_{50\%}$		$D_{2\ cm}$ (%)		$V_{20\ Gy}$ (%)		PTV (cc)
Deviation		Deviation		Deviation		Deviation		
None	Minor	None	Minor	None	Minor	None	Minor	
<1.25	1.25–1.40	<12	12–14	<65	65–75	<5	5–8	0–20
<1.15	1.15–1.25	<9	9–11	<70	70–80	<6	6–10	20–40
<1.10	1.10–1.20	<6	6–8	<70	70–80	<10	10–15	>40

Source: Hurkmans et al., Radiation Oncology 2009, 4:1

Abbreviations

SABR	Stereotactic ablative radiotherapy
OS	Overall survival
PFS	Progression-free survival
QOL	Quality of life
FACT-G	Functional Assessment of Cancer Therapy: General
EQ-5D-5L	EuroQol 5-Dimension 5-Level
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
ILD	Interstitial lung disease
GI	Gastrointestinal
MRI	Magnetic resonance imaging
FDG	18-Fluorodeoxyglucose
PET	Positron emission tomography
PSMA	Prostate-specific membrane antigen
AST	Aspartate transaminase
ALT	Alanine transaminase
GGT	Glutamyl transferase
INR	International normalized ratio
RFA	Radiofrequency ablation
CBCT	Cone beam computed tomography
PTV	Planning target volume
OAR	Organ at risk
4D-CT	4-Dimensional computed tomography
QA	Quality assurance
GTV	Gross tumor volume
CTV	Clinical target volume
PRV	Planning organ at risk volume
3D	3-Dimensional
VMAT	Volumetric modulated arc therapy
CDK	Cyclin-dependent kinase
RECIST	Response Evaluation Criteria in Solid Tumours
DSMC	Data safety monitoring committee
FFPE	Formalin-fixed paraffin-embedded
ctDNA	Circulating tumor DNA

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Protocol Version
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Authors' contributions
The initial draft of the protocol was prepared by DAP, RJMC, AA, and FS. All authors subsequently provided important feedback and made substantive revisions to the work. All authors have provided final approval of the manuscript.

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Funded through philanthropic donations to the London Health Sciences Foundation, and through grant funding awarded to DAP from the Ontario Institute for Cancer Research. This protocol was peer reviewed as part of an application to the Canadian Cancer Clinical Trials Network (3CTN). The funding bodies had no role in study design or writing of this report and will not be involved in data collection, data analysis, or data interpretation, writing of later reports, or the decision to submit any reports for publication. The first author (DAP), second author (MEG), and statistician (AW) will have full access to the data, vouch for the integrity of the data and the adherence to the study protocol, and will be responsible for the decision to submit the manuscript.

Availability of data and materials
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethics approval was granted from the Ontario Cancer Research Ethics Board (#4334), and will be obtained in all other jurisdictions that open the trial. Written informed consent will be obtained from all participants. Consent will be obtained at individual participating institutions by study investigators or clinical trials staff members.

Consent for publication
Not applicable.

Competing interests
David Palma reports research funding from the Ontario Institute for Cancer Research, royalties from UptoDate.com, and has a consultant role with equity with Need Inc, unrelated to the current study. Meredith Giuliani reports participation in advisory boards for AstraZeneca and Bristol Myers Squibb, unrelated to the current study. Stephen Harrow has received honoraria from AstraZeneca, Pfizer, and Takeda Pharamaceuticals, has consulted for AstraZeneca, and has received travel, accommodations and expenses reimbursements from AstraZeneca and Takeda Pharmaceuticals, unrelated to current study. Houda Bahig reports research grants from Varian Medical Systems, research grants and honoraria from AstraZeneca, and honoraria from Sanofi, unrelated to the current study. Robert Olson reports grant funding from Varian Medical Systems, and has a consultant role with equity with Need Inc, unrelated to the current study. Michael Lock reports consulting fees from Bayer and Tersera, and honoraria from Knight Therapeutics, Abbvie and Eisai, unrelated to the current study. Glenn Bauman reports research grants from the Ontario Institute for Cancer Research, participation in advisory boards for Advanced Accelerator Applications, and is the Clinical Lead, CTP for the Ontario Institute for Cancer Research, unrelated to the current study. Benjamin Lok reports research grants from Pfizer, and research grants, honoraria, and non-financial support from AstraZeneca, unrelated to the current study. Rachel Glicksman reports research grants from Astellas and TerSera, and honoraria from Bayer, TerSera, Knight Therapeutics and Tolmar. Christopher Goodman reports participation in advisory boards for AstraZeneca and a consultant role with equity with Need Inc, unrelated to the current study. Lucas Mendez reports research grants from the Terry Fox Research Institute, Academic Medical Organization of Southwestern Ontario (AMOSO) Opportunities, Ride For Dad (London, Ontario), Abbvie CARO Uro-Oncologic Radiation Awards (ACURA), Academic Medical Organization of Southwestern Ontario (AMOSO) Innovation, and Varian Medical Systems, and has received honoraria from Knights Therapeutics, and has participated in a data safety monitoring board for the London Regional Cancer Program, unrelated to the current study. All other authors report no competing interests.

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