Author’s response to reviews

Title: Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4-10 Oligometastatic Tumors (SABR-COMET-10): Study Protocol for a Randomized Phase III Trial

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Dear Dr. Gummlich,

We thank the reviewers for their constructive comments, which we feel have strengthened the manuscript. All comments are addressed on a point-by-point basis below.

Thank you for also noticing that we omitted one author name in the online system (Dr. Stephen Harrow, who was listed on the manuscript title page). We have made that correction online.

Thank you again for considering our manuscript for publication.

Sincerely,

David Palma

Response to Reviewers

Madhur K. Garg, MD, MBA (Reviewer 1): This is a proposed phase 3 study to evaluate SBRT in patients with 4-10 metastatic sites. It is an interesting concept considering positive results in oligometas trials. How did they arrive at a median survival of 10 months in control arm?

RESPONSE

Thank you for the review.

Our estimate of a 10-month survival in the control arm is based on the results of the original SABR-COMET trial, wherein patients with 4-5 metastases in the control arm had a median survival of only 7 months. We inflated this estimate to 10 months, to increase our power to detect a difference if outcomes have improved based on improvements in standard of care.
systemic therapy since the original trial. If the true survival in the standard arm is substantially longer, then statistical power might be reduced.

We have added the text above to the discussion (page 42, final paragraph).

COMMENT

Statistics look too simplified considering the diverse patient population they are planning to enroll.

RESPONSE

SABR-COMET-10, like the original trial, is not designed to elucidate differences in outcomes based on the diverse histologies, and indeed they will all be grouped together. Although histology-specific trials may better be able to determine the impact of SABR for different types of cancer, such trials run the risk failure to accrual, as the number of eligible patients would be inherently smaller.

We have added this to the discussion (page 42, final paragraph):

“Inclusion of all histologies allows for more rapid accrual, and reduces the risk of failure due to poor enrollment, but will not allow us to elucidate differences in outcomes by histologic subtype.”

Ugur Selek, MD (Reviewer 2): The objective of this phase 3 trial is to assess the impact of SABR, compared to standard of care treatment, on overall survival, oncologic outcomes, and quality of life in patients with a controlled primary tumor and 4-10 metastatic lesions. I congratulate the authors for their effort to initiate this necessary trial.

I believe the study design will adequately test the hypothesis.

I would recommend to give more details about the allowed number of lesions treated in the Arm 1 "current standard of care treatment". Besides, other local treatments such as resection or radiofrequency ablation need to be documented for the allowed limits after randomization. If these details would be lacking, the analysis might be challenging.

RESPONSE

Thank you for the review. We have added the following to the discussion (page 42, final paragraph):

“As in the original SABR-COMET trial, in SABR-COMET-10 there is no specified limit to the number of lesions that can be treated with palliative local treatments (such as external beam
radiation) on the standard arm. Ablative treatments are not expected to be provided in Arm 1, unless considered standard-of-care (e.g. stereotactic radiation for brain metastases), and all such treatments delivered will be documented.”

COMMENT

Restaging within 12 weeks prior to randomization seemed not rationale due to repopulation of cancer in a patient with 4-10 metastases might be expedited in the given time frame. Therefore, 6 weeks for example might be fairer.

Additional criteria for staging might be needed such as for cranial contrast enhanced MRI, as slice thickness of 5-10 mm would probably miss metastatic lesions in comparison to an MRI with 1-3 mm slice thickness.

RESPONSE

Thank you. We considered a 6-week window for restaging scans, but opted for a 12-week window to be consistent with the original SABR-COMET trial, and because some of our previous trials have run into accrual difficulties when the window was too short. All centres involved in SABR-COMET-10 use MRI slice thickness of 1-3 mm as suggested.

COMMENT

I would recommend to add a composite plan for all metastatic sites treated, at least the organ treated, to evaluate the DVH to avoid any risk regarding OAR tolerance doses, such as treating a right adrenal gland and two liver metastases which might totally risk the volume of normal liver doses (such as ≥ 700 cc less than 15 Gy in 3 fractions

RESPONSE

This is indeed required as part of the pre-planning, as reflected in the dose constraints for parallel structures such as the liver.

Shalini Kavita Vinod (Reviewer 3): This is a very well written study protocol to address a topic of considerable interest where high quality evidence is lacking. The emphasis on safe delivery of SABR (with priority given to OAR doses over tumour coverage, peer review of treatment plans and QA) is important given previous published reports of treatment related mortality with SABR. The authors are also commended in including translational endpoints.

RESPONSE

Thank you for the review and the positive feedback.
Rodney Wegner (Reviewer 4): This is a well-written, well-designed trial from experts on the topic. The protocol includes a nice summary of the data to date, as well as rationale for designing/performing this study in a setting of 4-10 metastatic lesions. The criteria are well-defined but not too constricting, and the multi institutional nature of the trial will help allow for accrual to be met. The outcomes are defined well, and I appreciate that safety is given great importance with no allowable exceeding dose constraints given the nature of the patient population.

I would suggest acceptance with no edits/revisions.

RESPONSE: Thank you for the review and the positive feedback.

Roy Decker, MD (Reviewer 5): The authors present a planned/ongoing multi-institutional phase III trial of comprehensive SABR for patient with limited metastatic disease, here defined as 4-10 metastatic lesions. This is an exciting and novel study which is a natural extension of the authors’ recently published phase II SABR-COMET study. The first SABR-COMET demonstrated improved OS (median 28 months versus 41 months for SABR), but did report 3 treatment-related deaths in the experimental arm. While the study included up to 5 metastatic sites, it was primarily populated with patients with 1 to 3 targets. The proposed 159 patient study includes a 2:1 randomization to SABR versus standard-of-care, and is appropriately powered for a primary endpoint of overall survival. The author have a companion SABR-COMET3 and plan to do secondary combined analyses, and there are included translational studies that are potential biomarkers.

This is an exciting study, though it may face some of the same challenges to accrual noted in previous randomized oligometastatic trials.

RESPONSE

Thank you for the review and the positive feedback. We have added the challenges to accrual to the discussion session (page 42, final paragraph):

We are optimistic that the pragmatic components of this trial, the large number of participating centres, and the presence of physician equipoise on this question will help to reduce the risk of poor accrual.