Statistical analysis plan

BONY-M

Stereotactic ablative radiotherapy (SABR) of bony metastases in patients with oligometastatic disease - A phase II study

Identifier: NCT05101824

Version 1 of 22 MARCH 2022

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Section 1 Administrative information

Title

Stereotactic ablative radiotherapy (SABR) of bony metastases in patients with oligometastatic disease - A phase II study (Bony-M)

Identifier

ClinicalTrials.gov Identifier: NCT05101824

Statistical analysis plan version

Version 2, 2023 February 10

Revision history: None.

The Version 1 of the statistical analysis plan was written after the completion of recruitment. The original trial protocol had defined the analysis plan briefly.

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Section 2 Introduction

Introduction

Please see protocol version 1.1, 1st MAY 2020. Stereotactic ablative radiotherapy (SABR) of bony metastases in patients with oligometastatic disease - A phase II study

Objectives

The Bony-M trial evaluates the efficacy and safety of SABR to bone metastases in patients with OMD, when pragmatically introduced into a daily clinical setting. In this study, all osseous oligo-metastases from solid tumours can be treated regardless of location, if organ at risk (OAR) constraints can be met. The approach is pragmatic as all pre-treatment evaluations are done by the referring oncologist and the party that approve the SABR plan.

The aim is to evaluate the Local control rate (LCR) at the radiated site 1- year post SABR with the hypothesis that the LCR is more than 75 % at one-year post SABR. Patients will have CT and clinical evaluation every 3-4 month after SABR according to the standard clinical follow-up program.

Primary endpoint

The local control rate one-year post SABR.

Secondary endpoints

- Rate of Symptomatic Skeletal Event (SSE) at the irradiated site(s)
- Progression-free survival (PFS)
- The rate of NCI CTCAE ≥ grade 3 toxicity
- Overall survival (OS)
- Time to progression (TTP) outside the radiation field
- LC rate two years post-SABR
- Pain reduction from baseline evaluated by "Numeric Pain Rating Scale (NPRS)" and analgesic consumption.
- Quality of life (QoL) measured with EuroQol EQ-5D-5L.

Toxicity, NPRS, analgesic consumption /antineoplastic treatment and EQ-5D-5L will be registered at baseline and at each follow-up.

Section 3: Study methods

Trial Design

Prospective, investigator-initiated, non-randimized phase II, multicentre study. The study has two dose levels of 30Gy or 37.5Gy in three fractions.

Sample size

At least 67 patients will be included in this study. Patients with de novo- and induced OMD, as well

as patients with oligo-recurrence or oligo-progression disease can be included. Simons two stage design is used for sample size calculation. The null hypothesis that the true 1- year local control rate is 60% and will be tested against a one-sided alternative.
The interim analysis will be performed after one year follow up of the first 27 patients. Recruitment will continue after inclusion of these 27 patients and will not wait the results of the interim analysis. If there are 17 patients or fewer with local control at one year in these 27 patients at the interim analysis after one-year follow up, the study will be paused, and the trial committee will discuss cessation of the study or dose adjustment (see section 9.3). Otherwise, 40 additional patients will be included and treated for a total of 67 treated patients. The null hypothesis will be rejected if 47 or more out of 67 patients have local control, at the radiated site, at 1-year after treatment. This design yields a one-sided type I error rate of 5% and power of 80% if the true 1- year local control rate is 75%. The last reported CTCAE classification status and response assessment will be registered in cases where the patient is lost for follow-up (e.g. succumbs from a "not treatment related" grade 5 event) prior to the 1-year assessment. A re-estimation of the required sample size will be made if more than 20% of patients fail to reach 1-year follow-up in the first stage of the trial in order to account for attrition and time-to-event analysis.

Framework
Primary endpoint: superiority against a one-sided alternative.

Statistical interim analysis and stopping guidance
Please see the sample size section

Timing of final analysis
Following study closure, data analysis of the primary endpoint will be performed 12 months after the last patient last treatment. Further analysis will be performed 2 and 5 years after the last patient has completed radiotherapy. Analysis of data in respect to secondary endpoints and exploratory studies might be analyzed at any point of time, at the discretion of the study group. Data will be kept in databases 10 years after the last patient is included.

Timing of outcome assessments

	Time point intervals (weeks)	Measurement of endpoints
Baseline	-4 ─ 0	QoL, CTCAE, PS, NPRS score, blood samples, radiographic assessment
2 weeks		CTCAE, PS, NPRS score, radiographic assessment
12 weeks	11 ─ 13	Local control rate, QoL, CTCAE, PS, NPRS score, blood samples, radiographic assessment
24 weeks	22 ─ 26	Local control rate, QoL, CTCAE, PS, NPRS score, blood samples, radiographic assessment
36 weeks	34 ─ 38	Local control rate, QoL, CTCAE, PS, NPRS score, blood samples, radiographic assessment
52 weeks	50 ─ 54	Local control rate, QoL, CTCAE, PS, NPRS score, blood samples, radiographic assessment
Abbreviation: QoL: quality of life by EQ-5D-5L and score of general health, CTCAE: common toxicity criteria of adverse events, PS: performance status, NPRS: numeric pain rating scale.		

Survival data for progression-free survival and overall survival will be collected at follow-up.

Section 4 Statistical principals

Confidence intervals and P values

Level of significance: $p < 0.05$ with no adjustment for multiplicity.

Confidence intervals are reported at 95 % limits (bound by zero) and calculated by the binominal distribution for rates and as per Kaplan-Meier method for time-to-event analyses.

Adherence and Protocol deviations

Definitions of protocol deviations:

- Study treatment
    - Delineation (GTV, CTV, and PTV)
    - Prescribed dose to GTV, CTV, and PTV
    - Dose constrains violations to organs at risk
- Missing follow-up time points intervals

Analysis populations

All analyses will be performed as intention-to-treat for patients who have receive any study treatment.

Safety analyses will be reported per event in a summary table. All CTCAE grades will be reported.

Section 5 Trial Population

Screening data
Not collected.

Eligibility
Inclusion criteria

- Histology or cytology proven non-haematological cancer.
- At least one lesion in the bones is required.
- ECOG performance status ≤ 2.
- ≥ 18 years old.
- Life expectancy > 6 months.
- GTV diameter ≤ 5 cm.
- In case of de novo OMD and OMD recurrence a maximum of 5 targets (including the primary tumour) in a maximum of 3 organ sites are allowed.
- In case of OPD * and induced OMD** only 3 metastases (including the primary tumour) are allowed.
- The metastatic lesion(s) must be visible on a CT- or MR- scan and suitable for treatment with SABR.
- All metastatic sites are treated or planned for ablative therapy (including surgery) - for OPD only the sites in progression is required to fulfil this criterion.
- A baseline scan within 28 days of inclusion (CT or PET- CT).
- For spine/paraspinal targets, an MR scan is mandatory, if epidural growth cannot be precluded on the baseline CT scan.
- No curative intended treatment option available.
- An ablative strategy should be deemed clinically relevant and is at the discretion of the treating physician to decide.
- Ability to understand and the willingness to sign a written informed consent document.

Exclusion criteria

- Patient cannot tolerate physical set up required for SABR.
- Uncontrolled intercurrent illness.
- Pregnancy
- Bilsky score ≥ 1b. If the patient is treated with surgery, a pre-operative Bilsky score ≥ 1b is an exclusion criterion as well. See appendix A for Bilsky score.
- Presence of myelopathy from the target area.
- Candidate for surgical treatment (determined by the institutions clinical oncologist, neurosurgeon or orthopaedic surgeon).
- For spine/paraspinal lesions where epidural growth cannot be precluded on the baseline CT scan: patients for whom an MR scan is contraindicated.
- Mechanical instability and/or fracture risk ***.
- For spine disease, involvement of ≥ three contiguous vertebrae.
- Uncontrolled disease in respect to malignant pleural effusion, ascites, lymphangitic carcinomatosis, pleural carcinomatosis or peritoneal carcinomatosis.
- Patients with uncontrolled brain metastases.
- If the patient has received previous radiotherapy, the combined dose at the radiation site must not exceed the dose constraints according to Appendix B in the study protocol

Foot notes to inclusion and exclusion criteria

* OPD	Progression of a limited number of metastatic lesions, while remaining metastases are controlled with systemic therapy. A maximum of 3 progressing metastases. This includes both progressive enlargement of a known metastasis and the development of a new metastasis.
*[2] Induced OMD	widespread metastatic disease is mostly eradicated by systemic treatment, but drug resistant clones are left behind, or the metastasis is located at a site not accessed by systemic therapy: Maximum 3 metastases. Only pre-existing metastases are allowed. The development of new metastases is not allowed
*[3]	Clinicians should consult a neurosurgeon, orthopaedic surgeon or radiologist and evaluate patients for stabilization prior to SABR if the following risk factors are observed: baseline VCF, significant lytic tumour burden, spinal malalignment, a SINS[1] > 6 or if the physician, for any reason, suspect the lesion to be unstable.

Recruitment, withdrawal and follow-up

We will report the following parameters in a modified consort diagram:

- Number of patients included in screening
    - Screen failures and description hereof
- Allocated treatment, i.e., 30Gy or 37.5Gy in three fractions
- Follow-up
    - Numbers lost to follow-up and reasons
    - Missing data
- No. of patients with data on specific time point

Baseline characteristics

- Biological sex (fraction)
- Median age and range
- Performance status (categorical)
- Charlson comorbidity score
- Primary tumor histology (categorical, four most common specified, the rest grouped as “other”)
- Oligo-metastatic classification (progressive, induced, de novo, and recurrence)
- Location of treatment target
- Soft tissue component
- Numbers of metastases treated
- Tumor median and range diameter (cm)
- GTV median and range (cm^3)
- Prescribed dose (37.5 or 30 Gy)
- Other ablative treatments for non-bony metastases
- Ongoing systemic treatment at baseline
    - No. of prior lines of systemic treatment

Radiation details:

Decisions on the two dose regimes are based upon the organs-at-risk constrains. The choice of dose regime depends on the proximity to OAR and the decision making should ideally follow the steps described here:

1. Dose regime one (12.5 Gy x 3 fractions) is recommended. Optimal GTV, CTV and PTV coverages, as described in this section, and constraints to OAR should be maintained
2. If this is not possible due to OAR constraints, the target coverage can be compromised to parts of GTV, CTV and/or PTV. It is recommended that the mean dose to the GTV and PTV should be at least 80% of the prescribed dose, i.e. 30 Gy for the GTV and 20 Gy for the PTV.
3. If this also is not possible, dose regime two (10 Gy x 3 fraction) should be explored.
4. If this still is not possible due to OAR constraints, the target coverage can be compromised to parts of GTV, CTV and/or PTV. It is recommended that the mean dose to the GTV and PTV should be at least 80% of the prescribed dose, i.e. 24 Gy for the GTV and 16 Gy for the PTV.
5. If none of the above-mentioned requirements can be achieved, the patient should be withdrawn from the study.

Reporting of the radiation details will follow the International Commission on Radiation Units and Measurements report no. 91 (IRCU91):

- Clinical decisions
    - Simulation: immobilization devices, accessories, planning image acquisition, and protocols
- Delineated volumes (cm^3)
    - GTV
    - CTV
    - PTV
- Description of treatment planning system
- Prescription
- Patient-specific QA
- Delivery
    - Treatment unit and energy, image verification device
- Dose documentation to target volumes
    - For the GTV, CTV, and PTV
        - Median dose (D50%)
        - Mean dose
        - D2%
        - D98%
        - D0.1cm3 (near max)
        - Dmax

    - Dose conformity, express by a ratio for
        - Conformity for the CTV and PTV coverage (CI100%)
            - Calculated by dividing the volume with 100% prescription isodose with the volume
        - Intermediate dose and fall off gradient (CI50%)
            - Calculated by dividing the volume with 50% prescription isodose with the volume of the total volume
    - Selected OAR and PRV will be presented, based on the OAR and PRV defined constrain (e.g., Spinal Cord Dmax point or esophagus D0.5cc)
- Dose compromises to the GTV, CTV and PTV
- Delineation violation

Section 6 Analysis

Outcome definitions

- Local control rate is defined as the absence of progression within the treated area (i.e., within or adjacent to the PTV) on imaging with CT -, MR -, or PET-CT - scan. Analysis is done at a lesion level, lesion by lesion. Patients are not censored from analysis in case of a new lesion outside the treated volume. We asses the response evaluation based on the interpretation of a radiologist with oncological experienced and based on the below definitions, which are modifications from the The University of Texas MD Anderson Cancer Center (MDACC) response criteria's:
    - Partial response (PR) is coded if there is unequivocal decrease in target lesions and/or development of a sclerotic rim or partial sclerotic fill for lytic lesions on CT.
    - Progressive disease (PD) is based on increase in tumor size interpreted by a radiologist.
    - Complete response (CR) is coded if there is complete disappearance of tracer activity on PET-CT, normalization of signal intensity on an MR scan or bone density on CT or/and complete sclerotic fill for lytic lesions on CT.
    - Stable disease (SD) is coded for any response other than CR, PR or PD.
- NCI CTCAE ≥ grade 3 toxicity
    - Early toxicity is defined as toxicity occurring within three months of radiotherapy completion.
    - Late toxicity is defined as toxicity occurring three months or longer after radiotherapy completion.
    - In time-to-event analysis of ≥ grade 3 toxicity, patients will be censored the date of death, study exit, or reached 12 months follow-up.
- Pain reduction NRPS from baseline evaluated by "Numeric Pain Rating Scale (NPRS)" and analgesic consumption.
    - A complete pain response (CPR) is defined as a pain score of 0 out of 10 at the treated site with no concomitant increase in analgesic intake
    - A partial pain response (PPR) is defined as a pain reduction of 2 or more at the treated site without analgesic increase, or an analgesic reduction of 25% with no increase in pain score or 1 point above baseline.
    - Pain progression (PP) is defined as an increase in pain score of 2 or more above baseline with stable analgesic intake or an analgesic increase of 25% with stable pain score.
    - An indeterminate response (Indet) is any response not captured in the above definitions.
- Symptomatic Skeletal Event (SSE) of the irradiated site is defined as a radiographically verification of fracture (vertebral or non-vertebral, pathological or non-pathological), within

or adjacent to the PTV of the irradiated site. The fracture must co-exist with one of the following symptoms/interventions:

  - progression in pain (according to definition in section 3.5)
  - development of neurological symptoms/ symptomatic spinal cord compression or a need for surgical intervention/ reirradiation. It should be concluded from the treating physician that the symptom/intervention is a result of the fracture.
  - Vertebral fractures include end plate–only fractures. Analysis is done at a lesion level, lesion by lesion. Patients with a pathological fracture before the radiation therapy, will not be included for analysis.

- Progression-free survival is defined as time from inclusion until disease progression or death. Progressive disease is noted based on the interpretation of the clinical oncologist, including radiographic, biochemical, and clinical assessments. Patients are censored at last follow-up or at study exit.
- Overall survival is defined as time from inclusion until death from any cause. Patients are censored at last follow-up or at study exit.
- Time to progression outside the radiation field is defined as the time from inclusion until progression outside the radiation field (i.e., outside and not adjacent to the PTV), determined by a CT -, MR -, or PET-CT – scan (based on the interpretation of the clinical oncologist, including radiographic, biochemical, and clinical assessment).
- Metastases are considered non-spine if they are located outside of the vertebral column or sacrum
- Contiguous lesions treated within one volume represents one target.

Analyses methods

Endpoint variable	**Type**	**Statistics**	**Confidence interval 95%**
Local control rate (primary)	Time-to-event	Kaplan-Meier (event: local progression, censoring: study exit, death, or last obtained radiographic assessment). Analysis at lesion-per-lesion. Follow-up by Reverse Kaplan-Meier	Kaplan-Meier method.
NCI CTCAE ≥ grade 3 toxicity	Rate, %	Descriptive, patient-per-patient, within 12 weeks and one year	Binominal distribution when applicable* (bound by zero)
Pain response	Categorical (CR,PR,PP, Indet)	Descriptive, response rates, two-groups of CR+PR and PP or Indet at 12 weeks and 52 weeks	Binominal distribution when applicable*

		follow-up. Comparison between timepoints with Mc Nemar test (paired samples).	
Rate of Skeletal event (SSE)/Rate of fractures	Time-to-event, rate	Rate at time point, cumulative incidence (Kaplan-Meier)	Kaplan-Meier
PFS and OS	Time-to-event	Kaplan-Meier (Follow-up by Reverse Kaplan-Meier)	Kaplan-Meier**
Time to progression	Time-to-event	Kaplan-Meier, cumulative incidence	Kaplan-Meier
QoL EQ-5D-5L	Categorical (index), and Visual analog scale	As per described in EQ-5D-5L guidelines. Combined index is calculated using Denmark as reference (CrossWalk from the 3D value set). Changes in EQ-index value and VAS-score over time (repeated measurement) will be analyzed with linear mixed-effect model with random intercept for each patient. The model will be chosen based on adherence to model assumptions (e.g., linearity and distribution). Data will be presented in plots of all data and for individual patients. Censored regression models (Tobit) will be used to adjust for the potential ceiling effect of the index score. Paired observations of changes per EQ-5D domains: probability of superiority.	

*Clopper Pearson method.

**Log-rank test for subgroup analysis.

We will report changes in NPRS score with frequency plots of changes between timepoints.

A swimmers-plot will be used to illustrate the timeline for each patient regarding local control, PFS, systemic/local treatment, and overall survival.

Follow-up time will be calculated by the reverse Kaplan-Meier method to minimize the underestimation of follow-up time. (Reference: Schemper M, Smith TL. A note on quantifying follow-up in studies of. Control Clin Trials. 1996;17:343–6)

Double included patients

The BonyM protocol allowed participants to be included twice at the discretion of the treating oncologist. Double included participants were excluded at the second entry for time-to-event analyses (survival) and the

quality of life analyses. For lesion-by-lesion analyses of local control-rate (primary endpoint), all lesions will be included.

Additional analyses/Explorative analyses

- Delineation study (Difference in target volume definition of bone metastases: Dual energy CT versus conventional CT, MR versus CT, PET-MR versus CT and in intra/inter delineation).
- Subgroup analysis (outcome according to histological profile).
- Subgroup analysis (toxicity according to location of metastasis - spine metastasis versus nonspine metastasis).
- Description of the use of online treatment adaption to keep minimal doses to OAR.
- Frequency and extent of compromise in prescription dose and/or to target coverage (GTV/CTV/PTV) due to OAR constraints (6.2).

Missing data

Any missing data will be excluded from the analyses and no assumptions will be made.

In case of non-complete reporting of measurements, the follow assumptions are made:

- If the NPRS score is not given, but the patient is described without any pain and take no analgetic medication, the NPRS score is set to zero. All other cases, the NPRS is recorded as “not available”
- If CTCAE is not registered at a follow-up visit and the patients have not been admitted to a hospital in during this interval, the patient case is considered as having no grade ≥ 3 toxicity.
  The last reported CTCAE classification status and response assessment will be registered in cases where the patient is lost for follow-up (e.g. succumbs from a “not treatment related” grade 5 event) prior to the 1-year assessment. In other words, such patients will be recorded at one year according to the latest available toxicity and response assessment.
- If a CTCAE score is not registered but described in full details in the journal, the investigators will translate the symptoms into a CTCAE grading.
- If performance status is not registered but described in full details in the journal (e.g., no change), the investigators will translate the symptoms into a performance status grading.
- Missing data will not be imputed and QoL measures missing to single timepoints are not excluded from the models.
- Incomplete EQ-5D-5L questionaries will be excluded but the VAS score can be included.

CTCAE registering process

- All CTCAE grading > 0 will be registered at baseline
- Only changes in CTCAE gradings will be registered at the follow-up events.
- For every change in CTCAE grading, an end date must be registered on the baseline or follow-up visit for which the adverse event primarily was registered.

- If no start or end date is registered for the CTCAE grading, the following procedure will be conducted:
    a. If increasing CTCAE grading, the start date will be the day after the last visit registered at the current visit and this date must also be registered as the end date on the previous grading of this AE.
    b. If decreasing CTCAE grading, the start date will be the day of the current visit registered at the current visit and the end date of the previous grading of this AE must be one day before the current date.
    c. If an adverse event date is not registered at EOT the date should be the day after first radiotherapy fraction.
- If missing CTCAE registration and no CTCAE registration can be extrapolated from the clinical journal, the adverse event registration should be confined to registering if the patients has been hospitalized and/or SAE has occurred and complete the report.
- If the patient is lost to follow-up at a visit and therefore CTCAE registration is missing, this should be noted in the RedCap database.

Harms

Toxicity will be reported according to the National Cancer Institute, Common toxicity criteria of adverse events version 5 (CTCAE) and as adverse events. All adverse event will be classified as treatment related, possible related and not related at the discretion of the treating physician.
A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose, results in death or is life-threatening, is disabling, requires hospitalization (whether initial or prolonged and does not include planned hospitalization) or requires intervention to prevent permanent impairment/damage. Progression or deteriorating of malignancy during the study (including new metastatic lesions or death due to progression), will be part of the efficacy assessment and should NOT be reported as an AE/SAE. All grades of CTCAE will be reported per patient. Please see "Definition of endpoint-related concepts" for specific definitions of toxicity related endpoints.

Proposed main tables

Table 1 - Patient and treatment characteristics

		Spinal	Non-spinal	Total
Age	Mean (range)			
Sex	Male / Female			

OMD state* [#]	Recurrence			
	Progressive			
	Induced			
	De novo			
Primary diagnosis	Prostate cancer			
	Breast			
	Kidney cancer			
	Other			
Targets per patient [#]	1			
	2			
	3			
Total metastases at baseline				#
Location (lesion by lesion)				
	Vertebra			
	Costae			
	Pelvis…			
Baseline Cancer Treatment				
	Yes			
	No			
Treatment line at baseline				
	1. line			
	1. line			
	2. line			
	>3. line			

*OMD: oligo-metastatic disease.

Table of target prescribed per protocol and achieved target coverage

No patients		30Gy (n=#)	37.5Gy (n=#)	
Target volume				
GTV_{mean} [cm^3] *				
CTV_{mean} [cm^3]				
PTV_{mean} [cm^3] **				
	Dose prescription per protocol			
Target coverage				
GTV D 99% [%]	>95%			
GTV mean [%]	≥ 100%			
GTV D50% [%]				
PTV D 99% [%]	>67%			
PTV D50% [%]				

Table of CTCAE

Data set: All Treated Patients						
Number of patients (%) N=***						
Worst grade						
Patients with any AE	NR ** (**)	1 ** (**)	2 ** (**)	3 ** (**)	4 **(**)	Any grade
Patients with AE within category Category 1(1) Event 1 Event 2 Event 3 ... Category 2(1) Event 1 ...	**(**) **(**) **(**) **(**) **(**) **(**) **(**) **(**)	**(**) **(**) **(**) **(**) **(**) **(**) **(**) **(**)	**(**) **(**) **(**) **(**) **(**) **(**) **(**) **(**)	**(**) **(**) **(**) **(**) **(**) **(**) **(**) **(**)	**(**) **(**) **(**) **(**) **(**) **(**) **(**) **(**)	**(**) **(**) **(**) **(**) **(**) **(**) **(**) **(**)

(1) Patients may have more than one event within a category.

Table Quality of life assessment compliance

Period	Expected	Received (%)
Baseline	***	*** (**.*)
At 3 Months	***	*** (**.*)

At 6 Months	***	*** (**.*)
At 9 Months	***	*** (**.*)
At 12 Months	***	*** (**.*)

Statistical software

All statistic calculations will be performed using R statistics (RCRAN project, version 4.03) with appropriate survival packages ("survival"), linear mixed model package "lmer4" and the "eq5d" package for calculating the QoL index score (with reverse crosswalk for EQ-5D-5L).