Clinical Protocol

Phase III randomized trial for high-risk asymptomatic or minimally symptomatic bone metastases: Early radiotherapy versus observation (HERMES trial)

Protocol number:	CTO23032GZA
Protocol version and issue date:	V3.0 07-OCT-2024
Sponsor:	Ziekenhuis aan de Stroom vzw Kempenstraat 100 2030 Antwerpen
Study responsible physician:	Dr. Charlotte Billiet

HERMES CLINICAL TRIAL

TARGETING HIGH-RISK BONE METASTASES

Clinical Trials Oncology

Ref.Nr.: P.01-S.23

Versie: 6.0

Statement of compliance

This study will be conducted in compliance with this clinical study protocol, the current International Conference on Harmonization and the guidelines for Good Clinical Practices (ICH-GCP), the principles of the Declaration of Helsinki (version 2002) and any applicable regulatory requirements. Enrolment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential subjects.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled subjects may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study subjects.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

Confidentiality Statement

This document and its contents are the property of and confidential to ZAS vzw. Any unauthorized copying or use of this document is prohibited.

Sponsor's approval

Protocol title: Phase III randomized trial for high-risk asymptomatic or minimally symptomatic bone metastases: Early radiotherapy versus observation (HERMES trial)

Version number and date: v3.0 07-OCT-2024

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated below.

Sponsor Representative:

Signature: Hendrika (Willeke) Dijkhoffz (10 okt. 2024 22:46 EDT) Date: 10-okt.-2024

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Name: Charlotte Billiet

Maatschappelijke zetel: Ziekenhuis aan de Stroom vzw - Kempenstraat 100 – 2030 Antwerpen - www.zas.be - BTW BE 0862.382.656

Investigator agreement

Protocol title: Phase III randomized trial for high-risk asymptomatic or minimally symptomatic Bone metastases: Early RAdiotherapy Versus Observation (HERMES trial)

Version number and date: v3.0 07-OCT-2024

I have read the protocol, appendices, and accessory materials related to HERMES and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the subjects under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2)
- To obtain approval for the protocol and all written materials provided to subjects prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all subjects enrolled at my study site prior to initiating any study specific procedures or administering investigational products to those subjects
- To maintain records of each subject's participation and all data required by the protocol

Signature: _____ Date: _____

Name: _____

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Appendix 1: Numeric Pain Rating Scale (NRS) Append relevant information.

Appendix 2: EORTC QLQ-C15-PAL

Appendix 3: EuroQol Group EQ-5D-5L questionnaire

Appendix 4: National Cancer Institute Common Terminologie Criteria for Adverse Events (NCI-CTCAE)

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Appendix 6: Spinal instability neoplastic score (SINS) [Fourney et al]

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Appendix 8: Mirels score [Mirels et al]

List of abbreviations

BTA: Bone-Targeted Agents

CT: Computed Tomography

CTCAE: Common Terminology Criteria for Adverse Events

CTV: Clinical Target Volume

eCRF: electronic case report form

ESCC: Epidural spinal cord compression

FU: Follow-up

GTV: Gross Tumor Volume

HR: Hazard ratio

ICF: Informed Consent Form

IEC: Independent Ethics Committee

IMRT: Intensity-Modulated Radiation Therapy

KPS: Karnofsky Performance Score

LAR: legally authorized representative

MRI: Magnetic Resonance Imaging

NRF prognostic score: Number of Risk Factors prognostic score

NRS: Numeric Pain Rating Scale

OAR: Organs At Risk

PET: Positron Emission Tomography

PFS: Pain-Free Survival

PRO: Patient Reported Outcome

PTV: Planning Target Volume

QoL: Quality of Life

RT: Radiation Therapy

SABR: Stereotactic Ablative Body Radiation

(S)AE: (Serious) Adverse Event(s)

SOE: Schedule Of Events

SINS: Spinal Instability Neoplastic Score

SSE: Symptomatic Skeletal Event

SUSAR: Suspected Unexpected Serious Adverse Reaction

VMAT: Volumetric Modulated Arc Therapy

Amendments

Protocol version	Issue date
Original protocol	18-MAR-2024
Amendment 1	25-SEP-2024
Amendment 2	07-OCT-2024

Amendment 1 (25-SEP-2024)

The purpose of this amendment is:

- To implement changes to the original protocol based on feedback from experts of the ethical committees.

The key changes are summarized in the table below:

Section number and name	Description of change and brief rationale
Confidentiality statement Sponsor's approval Study synopsis Administrative structure 8.2.3. Investigator reporting of an (S)AE to the sponsor	**Description:** Throughout the protocol, all information regarding GasthuisZusters Antwerpen vzw (GZA vzw) was replaced by information regarding Ziekenhuis Aan de Stroom vzw (ZAS vzw). **Brief rationale:** When the initial submission of the documents to the ethical committee occurred, the sponsor of the HERMES study was GZA vzw. From 01-AUG-2024 on, GZA has merged with ZNA to ZAS vzw (Ziekenhuis Aan de Stroom), resulting in ZAS acting as sponsor of the HERMES study.
Study synopsis Schedule of events (footnote a of Table 1) Section 1. Background & Rationale Section 2. Study objectives and endpoints (Table 2) Section 3.1 General scheme of study design	**Description + brief rationale** The following sentence was added to section 1 "Background and Rationale" (page 19) to clarify that preventive radiotherapy is already being applied based on experience/"expert opinion" in case of asymptomatic/minimally symptomatic high-risk bone metastases: "Currently, preventive radiotherapy for high-risk asymptomatic of minimally symptomatic

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Section 5. Study intervention: 5.1. Description 5.2. Allocation to treatment groups and blinding Section 6.1.2. Treatment planning and treatment period Section 7.2. Efficacy evaluations Section 9.3. Statistical methods for analysing primary and secondary outcomes	bone metastases occurs by physician's choice and experience as phase 3 scientific evidence is missing." In section 5.1, the following underlined words were removed: : "Upfront preventive RT <u>that is not considered part of standard of care</u> is not allowed." as preventive radiotherapy is already being applied based on experience/"expert opinion" in case of asymptomatic/minimally symptomatic high-risk bone metastases. In Figure 1 "standard of care" was replaced by "systemic therapy / observation". In the entire protocol, both study arms are now referred to as follows: Arm A = Observational arm = Systemic therapy/observation Arm B = Upfront RT arm = Upfront RT plus systemic therapy/observation
Section 9.4. Interim analyses	**Description** The following underlined words were added: "After 2 years, a blinded interim analysis is planned to estimate the event rate <u>by our statistical expert team</u>.". **Brief rationale** These words were added to clarify who will perform the blinded interim analysis (i.e. our statistical expert team).

Amendment 2 (07-OCT-2024)

The purpose of this amendment is:

- To specify that only (S)AE related to the bone metastatic disease or related to radiotherapy (only applicable for patients in arm B) must be reported in the eCRF.
- To add that "impending pathologic fracture for which prophylactic stabilization is recommended, characterized by Mirels score of ≥9 [Mirels et al]" is also an exclusion criterion.
- To correct that the Karnofsky performance score must be determined at screening and during follow-up visits instead of the ECOG value.

- To clarify that the posterior elements of the spine consist of the pedicles, laminae, facets (articular processes), transverse processes, and the spinous process.
- To clarify that all SSE's need to be recorded in both study arms i.e. SSEs related to any bone metastasis (exception: SSE's in bone metastases that were already treated with surgery or RT before study participation).
- To specify that patients in the upfront RT arm developing new minimally symptomatic or asymptomatic high-risk bone metastases during study participation are strongly advised to further be treated with preventive RT.
- To resolve inconsistencies with the eCRF

The key changes are summarized in the table below:

Section number and name	**Description of change and brief rationale**
Study synopsis Section 4.2 Subject inclusion criteria	**Description** In the study synopsis (Key inclusion and exclusion criteria) and in section 4.2 (Subject inclusion criteria), the following sentence was added to the high-risk definition: "<u>The posterior elements of the spine consist of the pedicles, laminae, facets (articular processes), transverse processes, and the spinous process.</u>". **Brief rationale** As a definition of "high-risk" is "disease in vertebrae of the junctional spine (C1-2, C7- T1, T12-L1, L5-S1) and/or disease with posterior element involvement or epidural extension (Bilsky epidural compression score 1a-3)", a sentence was added to clarify which parts the posterior elements of the spine consists of.
Protocol synopsis Subject exclusion criteria	**Description** The following underlined words were added to the fourth exclusion criterion: "Bone lesion complicated with a pathological fracture <u>or impending pathologic fracture for which prophylactic stabilization is recommended, characterized by Mirels score of ≥9 [Mirels et al] (see appendix 8)</u>" Moreover, appendix 8 "Mirels score" was added to this protocol.

	Brief rationale "impending pathologic fracture for which prophylactic stabilization is recommended, characterized by Mirels score of ≥9" is an exclusion criterion for participation in the HERMES study. As this was not yet mentioned in this study protocol, it was added with this amendment.
Study synopsis Section 2. Study objectives and endpoints Schedule of events (footnote j) Section 6.1.1. Screening period Section 9.3. Statistical methods for analysing primary and secondary outcomes Section 7.1. Screening evaluations and measurements Section 8.1.4. Causal relationship of an AE/SAE to the intervention Section 8.2.2. Period for collecting AE and SAE information Appendix 8	**Description** The following sentence was added to the study synopsis (study objectives and endpoints), to section 2 "Study objectives and endpoints" and to section 9.3 "Statistical methods for analysing primary and secondary outcomes": "Only adverse events that are related to the bone metastatic disease or related to the radiotherapy (only for patients in arm B) will be reported in the eCRF." The following words were added to footnote j of the schedule of events: "Note that only (S)AE related to the bone metastatic disease or related to radiotherapy (only applicable for arm B) must be reported in the eCRF". In section 6.1.1. "Screening period" the following underlined words were added: "Reporting of adverse events <u>that are related to the bone metastatic disease or related to the radiotherapy (only for patient in arm B)</u> as measured with NCI-CTCAE v5.0 (see appendix 4)" A new sub-section was added to section 7.1 "Screening evaluations and measurements", more specifically a sub-section entitled "7.1.9. Assessment of (serious) adverse events ((S)AE) during screening". The following text was added to the section 8.1.4. "Causal relationship of an AE/SAE to the

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	intervention": "Furthermore, the investigator will assess the relationship between the bone metastatic disease and each occurrence of each AE/SAE. Only AE/SAE that are related to the bone metastatic disease or related to radiotherapy (only applicable for patients in arm B) will be reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (see appendix 4)." Moreover, it was corrected that the relationship of each AE/SAE to the study intervention should be characterized using one of the following: related to RT, related to bone metastatic disease or unrelated, instead of just related and unrelated. This was also adapted in Table 3. The unrelated (S)AE do not have to be reported in the eCRF. The following underlined words are added to section 8.2.2: "all (S)AEs <u>that are related to the bone metastatic disease or related to radiotherapy (only applicable for patients in arm B)</u> will be documented in both study arms." **Brief rationale** Only (serious) adverse events that are relevant for the study need to be reported in the context of the study. Hence only (S)AE's that are related to the bone metastatic disease or related to radiotherapy (only applicable for patients in arm B) need to be documented in the context of the study. This should avoid documentation of a long list of irrelevant symptoms, unnecessarily generating additional workload. Furthermore, section 7.1.9. was created to clarify that the assessment of (S)AE is also part of the screening.
Study synopsis Section 9.3. Statistical methods for analysing primary and secondary outcomes	**Description** The underlined words were added to the primary objective and endpoint in the study

Section 2. Study objectives and endpoints Section 7.2. Efficacy evaluations Schedule of events (footnote j)	synopsis: "To assess whether early preventive radiation of the high-risk asymptomatic or minimally symptomatic bone metastases in patients with metastatic cancer can decrease the number of symptomatic skeletal related events (SSEs) by measuring the time to an SSE in any bone metastasis or death due to any cause." Similarly, the underlined words were added to the following sentence in section 9.3. "Statistical methods for analyzing primary and secondary outcomes": "The primary endpoint is time until the occurrence of SSE in any bone metastasis or death from the date of randomization whichever occurs first." Moreover, the underlined words were added to the primary endpoint in section 2 Study objectives and endpoints: "Time to a symptomatic skeletal related event (SSE) in any bone metastasis or death due to any cause." The following paragraph was added to section 7.2. Efficacy evalutions: "All SSE's will be recorded in both study arms. Patiens in the upfront RT arm may develop an SSE in a bone metastasis that was not previously included in the study, which also needs to be registered. An exception are SSE's in bone metastases that were already treated with surgery or RT before study participation." In footnote j of the schedule of events, the following underlined words were added: "Note that only (S)AE related to the bone metastatic disease or related to radiotherapy (only applicable for arm B) must be reported in the eCRF and that all SSE need to be registered in both study arms, including an SSE in a bone metastasis that was not previously included in the study (only applicable for arm B). An exception are SSE's in bone metastases that were already treated with surgery or RT before study participation."

	Brief rationale: These additions should clarify that ALL SSE need to be registered and that the primary endpoint is the time to an SSE IN ANY BONE METASTASIS or death due to any cause. It is for example possible an SSE occurs on another bone location than the ones enrolled in the study. Such an SSE also needs to be registered and counts for the primary endpoint.
Schedule of events (footnote l) Section 7.2. Efficacy Evaluations	**Description:** The following sentence was included as a footnote (l) in the schedule of events and was added to section 7.2. Efficacy Evaluations: "Patients in the upfront RT arm developing new minimally symptomatic or asymptomatic high-risk bone metastases during study participation are strongly advised to further be treated with preventive RT. Details concerning the characteristics of these new high-risk metastases as well as details regarding the preventive RT must be captured in the eCRF." **Brief rationale** These additions should clarify that patients in the upfront RT arm developing new minimally symptomatic or asymptomatic high-risk bone metastases during study participation are strongly advised to further be treated with preventive RT and that details must be captured in the eCRF.
Section 6.1.1. Screening Period Section 6.1.3. Follow-up Period Section 7.1.4. Karnofsky Performance Score (KPS) Section 7.3. Safety evaluation Schedule of events Appendix 5	**Description:** The ECOG performance status was replaced by the Karnofsky Performance Score at Screening and during the follow-up visits. **Brief rationale** ECOG Performance Status and Karnofsky Performance Score (KPS) both "measure" the patient's functional status/level of functioning.

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	As determination of the KPS is necessary for determining the NRF score, it was decided to determine the KPS instead of the ECOG value at screening and during the follow-up visits in order to standardize the protocol to avoid confusion.
Section 7.1. Screening evaluations and measurements Section 5.3. Treatment compliance and adherence Schedule of events (footnotes j and h)	**Description** In section 7.1, date of diagnosis of metastatic disease and the number of metastases at the time of the screening visit were added as a part of medical history. Moreover, it was corrected that the characteristics of the high-risk bone metastasis(es) include the total number of bone metastases, the location of the high-risk bone metastases (high-risk definition) and the number of metastases enrolled. In section 5.3 “Radiation technique used” and “fractions and dose that were originally planned” (in case of early termination of RT) were added as RT parameters to be collected and captured in the eCRF. The following was added to section 5.3: “Furthermore, at the end of the treatment period it will be documented in the eCRF whether the patient received observation or systemic therapy. In case systemic therapy was used, the following information will be recorded: - Name of systemic therapy - Start date systemic therapy - Whether systemic therapy was interrupted for RT (and if applicable the duration of the interruption)” The following sentence was added to footnote I of the schedule of events: “More specifically, the hospital admission date and date of discharge will be recorded as well as whether the hospitalization is related to an SSE (if yes, it should be specified to which SSE).”

	The following was added to footnote h of the schedule of events and to section 6.2.: “These assessments must be documented in the eCRF. Furthermore, the type of SSE (e.g. symptomatic pathological fracture,…) needs to be registered. In case of fracture or compression, the location and planned treatment must also be documented. In case of RT or surgery, the location and reason must be registered. ” **Brief rationale** These corrections/additions were made to make the information in the protocol consistent with the information that will be documented in the eCRF.
Section 7.1. Screening evaluations and measurements	**Description** It was removed that the location of metastases on other locations than bone need to be registered in the eCRF. **Brief rationale** This information will not be registered in the eCRF.

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Study synopsis

Protocol title:	Phase III randomized trial for high-risk asymptomatic or minimally symptomatic bone metastases: Early radiotherapy versus observation
Acronym:	HERMES
Protocol number:	CTO23032GZA
Sponsor:	Ziekenhuis aan de Stroom vzw Kempenstraat 100, 2030 Antwerp, Belgium +32 (0)3 443 37 59
Study responsible physician:	Dr. Charlotte Billiet Iridium Netwerk Department of Radiation Oncology Oosterveldlaan 22 2610 Wilrijk
Phase:	III
Study design:	Multicenter randomized phase III trial
Medical condition or disease under investigation:	High-risk asymptomatic or minimally symptomatic bone metastases
Intervention:	Early, upfront radiation therapy for asymptomatic or minimally symptomatic bone metastases.
Number of subjects:	120
Length of participation:	2 years
Key inclusion and exclusion criteria:	**Inclusion criteria** - Histologically confirmed solid tumor malignancy (with polymetastastic spread (more than 3 metastases)) - High-risk bone metastasis(es) that is (are) asymptomatic or minimally symptomatic: • Asymptomatic or minimally symptomatic is defined as follows: o Numeric Pain Rating Scale (NRS) score ≤2 • High-risk is defined as follows: o Bulky site of disease in bone (diameter ≥ 2 cm)

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	○ Disease involving the hip (acetabulum, femoral head, femoral neck), shoulder (acromion, glenoid, humeral head), or sacroiliac joints ○ Disease in long bones with cortical involvement of >1/3 in proportion to the diameter of the bone (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpals, phalanges) ○ Disease in vertebrae of the junctional spine (C1-2, C7- T1, T12-L1, L5-S1) and/or disease with posterior element involvement or epidural extension (Bilsky epidural compression score 1a-3) [Bilsky et al]. The posterior elements of the spine consist of the pedicles, laminae, facets (articular processes), transverse processes, and the spinous process. - Number of Risk Factors (NRF) prognostic score 0-2 (see section 5.1) - Age ≥ 18 years - Ability to provide informed consent (either by the patient or by a legally authorized representative) - A female participant is eligible to participate if she is not pregnant and one of the following conditions applies: Is not a woman of child bearing potential or A woman of child bearing potential must have a negative serum pregnancy test at screening (see Section 7.1.7) and must use a very effective method of birth control **<u>Exclusion criteria</u>** - Previous RT to the target treatment site(s) - NRF prognostic score 3 (see section 5.1) - Serious medical co-morbidities that preclude RT - Bone lesion complicated with a pathological fracture or impending pathologic fracture for which prophylactic stabilization is recommended, characterized by Mirels score of ≥9 [Mirels et al] (see appendix 8) - Spinal metastasis with SINS score >13 requiring upfront neurosurgical stabilization [Fourney et al]. - More than 5 high-risk asymptomatic or minimally symptomatic metastatic bone locations
Study objectives and endpoints:	**Primary objective and endpoint:**

	To assess whether early preventive radiation of the high-risk asymptomatic or minimally symptomatic bone metastases in patients with metastatic cancer can decrease the number of symptomatic skeletal related events (SSEs) by measuring the time to an SSE in any bone metastasis or death due to any cause. SSEs are defined as: - symptomatic pathological fracture - spinal cord compression leading to neurological deficit or pain - Indication for palliative radiotherapy (for bone pain, cord compression or (impending) fracture) - Indication for orthopedic surgery (for bone pain, cord compression or (impending) fracture) **Secondary objective and endpoint:** • To evaluate the need for hospitalization by comparing the number of **hospitalizations** related to the high-risk bone metastase(s) between systemic therapy/observation (arm A / observational arm) and upfront RT (arm B / upfront RT arm) from time of study randomization to date of death of any cause or last follow-up visit (24m after randomization date) or early end of participation in the study due to other reasons. • **To assess overall survival** from time of study randomization to date of death of any cause or last follow-up visit (24m after randomization date) • **To evaluate quality of life** using the EORTC QLQ-C15-PAL questionnaire (see appendix 2) and the EuroQol Group EQ-5D-5L questionnaire (see appendix 3) • **To evaluate acute** (if related to RT for patients in arm B **≤** 90 days after the last RT dose) **and late** (if related to RT for patients in arm B **>** 90 days after the last RT dose) **toxicity by assessing adverse events** in both study arms from the time of ICF signing to last follow-up visit (24m after randomization date), death of any cause or early end of participation in the study due to other reasons using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (see appendix 4). Only adverse events that are related to the bone metastatic disease or related to the radiotherapy (only for patients in arm B) will be reported in the eCRF.
Study duration:	48 months

Schedule of events

Table 1 Assessments during screening, treatment and follow up[i]

	Screening	Enrollment	Treatment period[a,h,l]		Follow-up period[h,l]	
Scheduling	**Within 3 weeks prior to randomization**			**Within 21 days after randomization date**	**1 month[g] after randomization date**	**3 months, 6 months, 12 months, 18 months and 24 months after randomization date**
Window					+/- 1 week	+/- 3 weeks
Required investigations:						
Informed Consent[b]	x					
Review Inclusion/Exclusion Criteria	x					
Demographics[c]	x					
Medical History	x					
Prior medications[d]	x					
Karnofsky performance score	x				x	x

	Screening	Enrollment	Treatment period[a,h,l]		Follow-up period[h,l]	
Scheduling	**Within 3 weeks prior to randomization**			**Within 21 days after randomization date**	**1 month[g] after randomization date**	**3 months, 6 months, 12 months, 18 months and 24 months after randomization date**
Window					+/- 1 week	+/- 3 weeks
Required investigations:						
High-risk metastase(s) characteristics	x					
Pain score per lesion (NRS scale)	x					
QLQ-C15-PAL questionnaire [e]	x				x	x
EQ-5D-5L questionnaire[e]	x				x	x
Pregnancy test in case of premenopausal female patients	x					
Randomization		x				
Adverse events assessments (NCI-CTCAE)[j]	x				x	x
Concomitant medications [f]					x	x
CT simulation and RT planning			x			
RT delivery				x		

	Screening	Enrollment	Treatment period[a,h,l]		Follow-up period[h,l]	
Scheduling	**Within 3 weeks prior to randomization**			**Within 21 days after randomization date**	**1 month[g] after randomization date**	**3 months, 6 months, 12 months, 18 months and 24 months after randomization date**
Window					+/- 1 week	+/- 3 weeks
Required investigations:						
Survival data[k]					x	x

a. Only patients in upfront RT arm B will undergo CT simulation and RT delivery. All patients in the study receive systemic therapy / observation. The received treatment will be documented in the eCRF.
b. Informed consent (from the patient or his/hers legally authorized representative [LAR]) must be documented before any study specific procedure, including procedures for screening, is undertaken.
c. Gender, year of birth and age will be recorded as part of the screening procedures.
d. Anticancer therapy, bone-modifying agents and pain medications (including corticoid therapy) within 7 days before screening visit will be recorded at screening. The dates of administration, method of administration, dosage, and reason for use will be included.
e. Health related quality of life parameters will be reported by subjects using the EORTC QLQ-C15-PAL and EQ-5D-5L questionnaires
f. All pain -and anticancer medications (including corticoid therapy) and bone-modifying agents used during the study will be recorded. The dates of administration, method of administration, dosage, and reason for use will be included.
g. A month can be 28, 29, 30 or 31 days, depending on the month.
h. Occurrence of an SSE during the study should be reported to the study team immediately. In case an SSE occurs, the assessments that should take place during the next follow-up visit, should be completed at that time point, preferentially within one week. These assessments must be documented in the eCRF. Furthermore, the type of SSE (e.g. symptomatic pathological fracture,…) needs to be registered. In case of fracture or compression, the location and planned treatment must also be documented. In case of RT or surgery, the location and reason must be registered. Afterwards, only survival data will be recorded on the date of the planned FU visits until 24m after the randomization date as well as possible occurrence of another SSE within 24m after the randomization date.

i. During the study (from time of study randomization to date of death of any cause or last follow-up visit (24m after randomization date) or early end of participation in the study due to other reasons), hospitalizations related to the high-risk bone metastase(s) should be documented in the eCRF. More specifically, the hospital admission date and date of discharge will be recorded as well as whether the hospitalization is related to an SSE (if yes, it should be specified to which SSE).

j. For each SAE, it should be evaluated whether it concerns an SSE. If it concerns an SSE, the SAE should be documented as such in the eCRF and the necessary actions should be taken (see footnote h). In case hospitalization occurs, it should be evaluated whether the hospitalization is related to the high-risk metastase(s) and this information should be documented in the eCRF. Note that only (S)AE related to the bone metastatic disease or related to radiotherapy (only applicable for arm B) must be reported in the eCRF and that all SSE need to be registered in both study arms, including an SSE in a bone metastasis that was not previously included in the study (only applicable for arm B). An exception are SSE's in bone metastases that were already treated with surgery or RT before study participation.

k. In case of discontinuation of a subject's participation without withdrawal of consent, only survival data will be collected at the remaining follow-up timepoints (i.e. 1m, 3m, 6m, 12m, 18m and 24m after randomization date) and the occurrence of an SSE will be registered in the eCRF if it occurs within 24m after the randomization date.

l. Patients in the upfront RT arm developing new minimally symptomatic or asymptomatic high-risk bone metastases during study participation are strongly advised to further be treated with preventive RT. Details concerning the characteristics of these new high-risk metastases as well as details regarding the preventive RT must be captured in the eCRF.

Administrative structure

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1. Background & Rationale

Bone metastases are common in patients with advanced cancers with an incidence of approximately 70% in breast, 85% in prostate, and 40% in lung and renal cancers [Huang et al]. **Skeletal complications** related to bone metastases may include pathologic fractures that may impair mobility and vertebral compression or fracture leading to spinal cord compressions that can result in numbness or weakness, urinary/fecal incontinence, or paralysis. These skeletal related events (SRE) are common in patients with solid tumors, with overall incidence rates of approximately 45%–65% in patients not receiving prophylactic antiresorptive therapy [Coleman et al]. The underlying pathophysiology, irrespective of primary tumor type and radiographic appearance, is a locally increased pathologic rate of bone resorption due to increased osteoclast activity [Roodman et al].

An SRE is considered as an objective and clinically relevant endpoint for the evaluation of preventive treatments in patients with bone metastases and is defined as radiation to bone, pathologic fracture assessed either clinically or through routine radiographic scans, surgery to bone, or spinal cord compression). In some recent phase 3 trials [Smith et al; Sartor et al; James et al] a new endpoint **termed symptomatic skeletal events (SSEs)** was used, defined as radiation to bone, symptomatic pathologic fracture, surgery to bone, or symptomatic spinal cord compression. In contrast with SREs, ascertainment of SSEs does not include scheduled radiographic assessments and may be more clinically relevant.

Denosumab and bisphosphonates are bone-targeted agents (BTA) that inhibit normal osteoclast-induced bone resorption. BTAs have already proven to prevent SREs or delay the time to SREs in solid tumors and multiple myeloma [Carrigan et al; Rosen et al]. **Bone-supportive agents have been demonstrated to reduce the number of SREs**, but SREs are still seen in more than 30% of patients [Smith et al]. Consequently, there remains a big unmet need in further preventing them.

SREs/SSEs are associated with pain progression and impaired **health-related quality of life** (HRQoL) and often trigger the need for analgesics, radiotherapy (RT) or surgery. In many cases, pain and quality of life cannot be fully restored with these measures. Conventional RT can achieve a clinically significant pain response in up to 80% of treated patients with a median response duration of 18–21 months [Oldenburger et al]. It is widely accepted as the standard of care for palliative treatment of uncomplicated metastatic bone pain, but is currently mainly applied once lesions become symptomatic [Steenland et al; Sze et al].

Our hypothesis is that early **RT for asymptomatic or minimally symptomatic high-risk bone metastases may have the potential to improve patient outcomes and quality of life** by reducing the number of SSEs.

A recent randomized phase II trial enrolled 74 patients to early palliative radiation versus standard of care alone to assess if early RT could decrease the incidence of SREs. Compared to standard of care, **RT resulted in a decrease in SRE incidence from 29% to 1.6% at 1 year**. Pain and need for hospitalizations were also decreased. Interestingly, RT also had a significant overall survival (OS) benefit (median OS 1y vs 1.67y (p=0.018)) compared to standard of care [Rosen et al].

Considering the striking results of this recently published phase 2 trial [Rosen et al], we will perform a **multi-centric randomized phase 3 trial to establish RT as a new treatment paradigm to prevent SSEs**. Currently, preventive radiotherapy for high-risk asymptomatic of minimally symptomatic bone metastases occurs by physician's choice and experience as phase 3 scientific evidence is missing.

We believe that preventing SSEs may have a direct impact on quality of life, cost reduction and maybe even overall survival. The benefits of palliative RT are its wide availability, its low costs and limited patient burden often in a single patient visit. In this trial, patients will be randomized to receive observation or systemic therapy or early RT in addition to observation or systemic therapy. The intervention in this study is early, upfront radiation therapy to asymptomatic or minimally symptomatic bone metastases. The aim of this trial is reducing the number of SSEs, inherently a **symptom-based endpoint.** Therefore, the hypothesis of the project is to decrease symptoms and side effects for each individual patient.

2. Study objectives and endpoints

The primary and secondary objectives and endpoints of the study are presented in Table 2.

Table 2: Objectives and endpoints for the Hermes trial

Objectives	**Endpoints**
Primary	
To assess whether early preventive radiation of the high-risk asymptomatic or minimally symptomatic bone metastases in patients with metastatic cancer can decrease the number of SSEs*.	• Time to a symptomatic skeletal related event (SSE) in any bone metastasis or death due to any cause.
Secondary	
• To evaluate the need for hospitalization related to the high-risk bone metastase(s) • To assess overall survival (OS) • To evaluate quality of life (QoL)	• The number of **hospitalizations** related to the high-risk bone metastases will be compared between systemic therapy/observation (arm A) and upfront RT (arm B) from date of study randomization to last follow-up visit (24m after randomization date), date of death of any cause or early end of participation in the study due to other reasons • **Overall survival** will be assessed from time of study randomization to date of death of any cause or last follow-up visit (24m after randomization date) • **Quality of life** will be compared between systemic therapy/observation (arm A) and upfront RT (arm B),

• To evaluate acute and late toxicity	using the EORTC QLQ-C15-PAL questionnaire (see appendix 2) and the EuroQol Group EQ-5D-5L questionnaire (see appendix 3) • **Adverse events** in both study arms will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (see appendix 4) from the time of ICF signing to last follow-up visit (24m after randomization date), date of death of any cause or early end of participation in the study due to other reasons. Only adverse events that are related to the bone metastatic disease or related to the radiotherapy (only for patients in arm B) will be reported in the eCRF.

*SSEs are defined as:

- symptomatic pathological fracture
- spinal cord compression leading to neurological deficit or pain
- Indication for palliative radiotherapy (for bone pain, cord compression or (impending) fracture)
- Indication for orthopedic surgery (for bone pain, cord compression or (impending) fracture)

3. Overall study design.

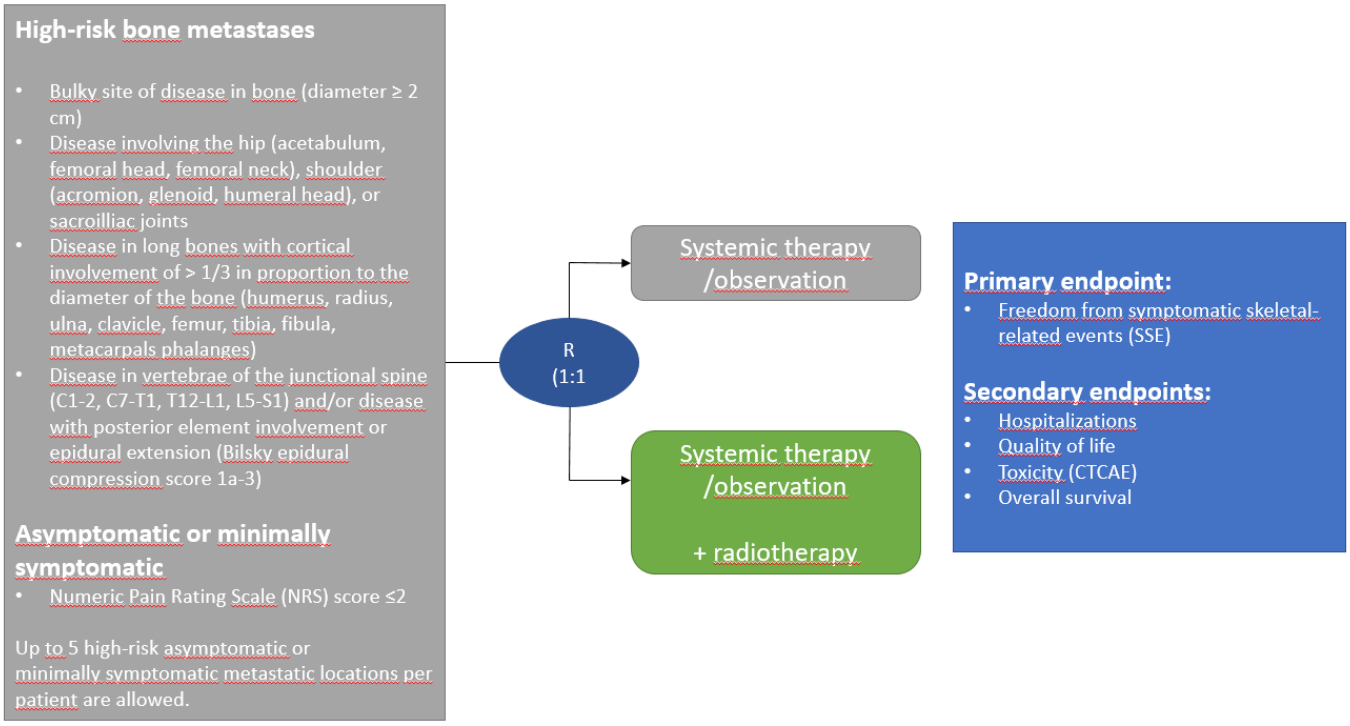
3.1 General scheme of study design

The HERMES study is a phase III randomized controlled trial to investigate if early, upfront RT for asymptomatic or minimally symptomatic high-risk bone metastases can prevent symptomatic skeletal events. The primary outcome is the time to a symptomatic skeletal event (SSE) or death due to any cause. Secondary outcomes are overall survival, early and late adverse effects, quality of life and need for hospitalization related to the high-risk bone metastase(s).

The study will be conducted in various centers (inter)nationally.

Participation in the HERMES study will comprise a screening period, during which the screening assessments must be completed. Eligible, consenting subjects will then be randomized (1:1) into one of two treatment arms: an observational arm (arm A) receiving systemic therapy / observation or an upfront RT arm (arm B) receiving upfront RT plus systemic therapy / observation. RT should take place within 21 days after date of randomization for subjects in arm B. Afterwards, onsite follow-up visits will take place at 1, 3, 6, 12, 18 and 24 months after date of randomization during which safety and efficacy are monitored.

The screening, treatment and follow-up schedules are presented in Table 1. A schematic presentation of the study design is shown in Figure 1.



Abbreviations: R = Randomization

Figure 1: Schematic representation of study design of the HERMES study.

3.2 Study duration, enrolment and number of sites

3.2.1 Duration of study participation

The total study duration will be 4 years, with an accrual period of 2 years. The total follow-up period will be 2 years for each patient.

3.2.2 Total number of study sites/total number of subjects projected

The HERMES study is a multicenter randomized trial. The total sample size of the study will be 120. We aim for randomization of a total of 96 patients (48 in each treatment arm) as a drop-out of 20% is assumed. More information with regard to the statistics can be found in section 9.

4. Study population

4.1 Definitions

Subjects officially enter the screening period following provision of informed consent either directly or via a legally authorized representative (LAR). Screening for eligible subjects will be performed within 3 weeks before randomization.

Eligible, consenting subjects will be enrolled to the study. Prior to enrollment of a subject, the following must occur:

- Confirmation that the subject has signed the informed consent form (ICF).
- Confirmation that the subject meets all of the inclusion and none of the exclusion criteria.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. Enrollment will occur only if the subject meets all study eligibility criteria and has been assessed by the Investigator as being an appropriate candidate for study participation. If there is a question about any of these criteria, the investigator must consult with the appropriate Sponsor representative and resolve any issues before enrolling a participant in the study. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before treatment such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

An enrolled subject is one who has been deemed eligible and has been assigned to a treatment group.

4.2 Subject inclusion criteria

To be included in this study, each subject must satisfy all the following criteria:

- Histologically **confirmed solid tumor malignancy** (with polymetastastic spread (more than 3 metastases))
- **High-risk bone metastasis**(es) that is (are) asymptomatic or minimally symptomatic [Rosen et al]:
  - Asymptomatic or minimally symptomatic is defined as follows:
    - Numeric Pain Rating Scale (NRS) score ≤2 for the specific lesion(s) (see appendix 1)
  - High-risk is defined as follows:
    - Bulky site of disease in bone (diameter ≥ 2 cm)
    - Disease involving the hip (acetabulum, femoral head, femoral neck), shoulder (acromion, glenoid, humeral head), or sacroiliac joints
    - Disease in long bones with cortical involvement of >1/3 in proportion to the diameter of the bone (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpals, phalanges)
    - Disease in vertebrae of the junctional spine (C1-2, C7- T1, T12-L1, L5-S1) and/or disease with posterior element involvement or epidural extension (Bilsky epidural

compression score 1a-3; see appendix 7) [Bilsky et al]. The posterior elements of the spine consist of the pedicles, laminae, facets (articular processes), transverse processes, and the spinous process.

- Number of Risk Factors (NRF) prognostic score 0-2 (see section 5.1)
- Age ≥ 18 years
- Ability to provide informed consent (either by the patient or by a LAR)
- A female participant is eligible to participate if she is not pregnant, and one of the following conditions applies:
  Is not a woman of child bearing potential or

A woman of child bearing potential must have a negative serum pregnancy test at screening (see section 7.1.7) and must use a very effective method of birth control

4.3 Subject exclusion criteria

A subject who meets any of the following criteria must be excluded from the study:

- Previous RT to the target treatment site(s)
- NRF prognostic score 3
- Serious medical co-morbidities that preclude RT
- Bone lesion complicated with a pathological fracture or impending pathologic fracture for which prophylactic stabilization is recommended, characterized by Mirels score of ≥9 [Mirels et al] (see appendix 8).
- Spinal metastasis with SINS score >13 (see appendix 6) requiring upfront neurosurgical stabilization [Fourney et al].
- More than 5 high-risk asymptomatic or minimally symptomatic metastatic bone locations

4.4 Study restrictions

Subjects will be informed and reminded of all study restrictions during recruitment, the informed consent process, and during screening and other scheduled assessments. Compliance with all restrictions will be required for the duration of the study.

4.4.1 Contraceptive requirements

Pregnant women are excluded; as well as women of child-bearing potential who are unwilling or unable to use a very effective method of birth control. Child-bearing potential is defined as follows: A woman is considered of child-bearing potential, i.e. fertile, following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Very effective methods of birth control are sterilisation and, in case of optimal use, condoms and hormonal contraception. However, no contraceptive is 100% reliable.

4.4.2 Other lifestyle considerations and study restrictions

No lifestyle restrictions apply.

4.4.3 Prior and concomitant therapies

Patients treated with prior or concomitant systemic therapy are eligible for this study. The decision for (dis)continuation is left at the discretion of the treating physician.

All pain medication (including corticoids), bone-modifying agents and anticancer therapy used within 7 days prior to the screening visit and through the end of the study will be recorded. The dates of administration, method of administration, dosage, and reason for use will be included. There are no restricted or prohibited medications.

4.5 Screen failures

A screen failure is a consented subject who has been deemed ineligible on the basis of one or more eligibility criteria or who has withdrawn consent prior to treatment assignment.

Patients who sign an informed consent but fail to start with treatment for any reason will be considered a screen failure. The reason for not starting with treatment will be recorded on the subject screening and enrollment log. Collection of information on screen failure is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials Publishing Requirements and to respond to queries from regulatory authorities. The required information includes date of consent, demography, screen failure details, eligibility criteria, and any (serious) adverse events.

Rescreening (*e.g*. for a metastasis in a different location) can be permitted in this study, after agreement between the investigator and the sponsor. The minimal number of procedures from the initial screening that should be repeated must be discussed with the study responsible physician.

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the Sponsor study-site contact for completeness. The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify all participants by participant identification number (see Section 5.2).

5. Study intervention

5.1 Description

Patients will be randomized (1:1) to receive either systemic therapy/observation (Arm A) or early RT plus systemic therapy / observation (Arm B).

Arm A:

The observational arm (Arm A) will include **observation or systemic therapy**, according to the treating physician's discretion. Systemic therapy may include continuation of the current systemic therapy or initiation of a new systemic therapy.

These patients will be able to receive palliative RT to progressed, painful lesions (an SSE) only at the time of symptom worsening (NRS> 2/10 or need for opioids) or determination of spinal cord compression with neurological symptoms or (high risk for) fracture requiring surgical intervention. Upfront preventive RT is not allowed.

Arm B:

The intervention in this study is **early, upfront radiation therapy** to asymptomatic or minimally symptomatic (defined as high-risk) bone metastases. Up to 5 high-risk asymptomatic or minimally symptomatic metastatic locations per patient are allowed.

The radiotherapy (RT) doses used will be in accordance with common practice palliative RT schedules. As such a single fraction of 8 Gy is considered for all patients, except for patients with a very good prognosis (NRF prognostic score 0-1) in which a higher dose will be used with SABR [Chow et al].

Table 3: Predictive model for estimation of median overall survival (OS): NRF-model [Chow et al].
Three variables:

- **Primary cancer type** **-> risk factor: non breast/prostate/lung cancer**
- **Site of metastases** **-> risk factor: metastases other than bone**
- **Karnofsky performance score (KPS)** **-> risk factor: KPS ≤60**

0-1 risk factors	median OS 64 weeks	95%CI: 37-undefined
2 risk factors	median OS 28 weeks	95% CI 22-34
3 risk factors	median OS 10 weeks	95% CI 8-13

Simulation:

All patients will be immobilized in a comfortable and stable position to irradiate the metastatic lesion(s). Support and/or immobilization devices will be used to increase patient comfort or to ensure set-up reproducibility. A planning CT scan will be acquired without intravenous contrast with <3mm CT slice thickness (1mm for SABR) encompassing the region of interest with sufficient margin for treatment planning, a typical scan length should extend at least 10 cm superior and inferior beyond the treatment field borders. The isocenter will be placed in the middle of the affected bone lesion.

Target volume definition:

1. *Conventional radiotherapy:*

The Gross Tumor Volume (GTV) will consist of the metastatic lesion(s) as visualized on CT. All available diagnostic imaging (PET-CT, MRI) will be used in order to delineate the target structures as accurate as possible.

A Clinical Target Volume (CTV) is delineated using a 5 to 10 mm margin on the GTV respecting the anatomical boundaries.
For spinal lesions, delineation of the whole affected vertebra is recommended as CTV.

The Planning Target Volume (PTV) will be created by using a 3-dimensional margin on the CTV to allow for daily set-up variance and organ motion. Margins depend on the radiation technique ranging from 5 up to 10 mm for 3D conformal low dose radiation.

Organs at risk (OAR) within 10 cm of the target volume will be contoured as visualized on the planning CT depending on the localization of the target lesion.

2. *SABR*:

The Gross Tumor Volume (GTV) will consist of the metastatic lesion(s) as visualized on CT. All available diagnostic imaging (PET-CT, MRI) will be used in order to delineate the target structures as accurate as possible.
For spinal lesions an MRI in treatment position is mandatory.

A Clinical Target Volume (CTV) is delineated using a 5 to 20 mm margin on the GTV respecting the anatomical boundaries [Nguyen et al].
For spinal lesions, delineation of the whole affected vertebra is recommended as CTV.

The Planning Target Volume (PTV) will be created by using a 3-dimensional margin on the CTV to allow for daily set-up variance and organ motion. Margins depend on the radiation technique ranging from 2-5 mm margins for bony lesions treated with SABR.
For spinal lesions, a PTV_high is created around the GTV and a PTV_low around the CTV respectively.

Organs at risk (OAR) within 10 cm of the target volume will be contoured as visualized on the planning CT depending on the localization of the target lesion. In case of SABR, a Planning Organ at Risk Volume (PRV) expansion will be added to the OAR for setup uncertainty or organ motion and all dose constraints apply for this PRV.

Bone metastases that are within 5 cm of each other will be treated as one site.

<u>Treatment planning:</u>

1. *Conventional radiotherapy:*

Standard fractionation will be 1x8 Gy. Although there is evidence in current literature that a single dose of 8 Gy is non-inferior in terms of pain control, there is no evidence for the current trial endpoint (development of SSE) so other fractionation regimens (e.g. 20 Gy in 5 fractions or 30 Gy in 10 fractions) are accepted and decided by the treated physician.

To minimize treatment time, the preferred treatment planning is rotational intensity-modulated radiation therapy (IMRT), i.e., volumetric modulated arc therapy (VMAT), using 6-MV photons. Conformal 3D-RT is also allowed in case of standard dose. Prescribing, recording and reporting of the doses will be consistent with the recommendations in Report 91 of the International Commission on Radiation Units and Measurements (ICRU) [ICRU et al].

In the standard setting, 95% of the PTV should receive 95% of the prescribed dose while near maximum dose (Dnear-max) in the PTV should not exceed 107%.

2. *SABR:*

For patients with a better prognostic outcome (NRF score 0-1) a higher dose will be delivered with SABR using either 1x20 Gy, 2x12 Gy, 3x10 Gy or 5x8 Gy (schedule will depend on the coverage and dose to OAR during treatment planning). However, dose can be changed towards a palliative dose when SABR is not expected to be safe (for example in case of high-risk bone lesions such as impeding bone fracture).
For spinal lesions, a a simultaneous integrated boost (SIB) planning will be used, where the high-dose PTV receives a higher dose in regard to the non-affected bone included in the low-dose PTV. SABR using a SIB technique will be delivered in 2 fractions of 12 Gy to the PTV_high and 2 fractions of 6 Gy to the PTV_low.

To minimize treatment time, the preferred treatment planning is rotational intensity-modulated radiation therapy (IMRT), i.e., volumetric modulated arc therapy (VMAT), using 6-MV photons. Conformal 3D-RT is also allowed in case of standard dose. Prescribing, recording and reporting of the doses will be consistent with the recommendations in Report 91 of the International Commission on Radiation Units and Measurements (ICRU) [ICRU et al].

In the SABR arm, the planning aim is to have 99% of the PTV receiving the prescription dose for an optimal target coverage. Because no violation of the OAR constraints nearby is allowed, covering of 90% (or at least 80%) is allowed to receive the prescribed dose. If this is not possible, an adaptation of the fractionation regimen is necessary towards a more fractionated treatment (radiobiological better than a decreased dose). Covering <80% will be reported as a minor protocol deviation.

Maximum PTV dose up to 140% is allowed but all dose > 105% should be contained within the PTV and preferably within the GTV. A dose fall-off outside the PTV extending into normal tissue structures should aim at 50% of the prescribed dose within 3 cm.

The OAR dose constraints for SABR will be in accordance with the recommendations from the report of the UK [Diez et al]. If a dose constraint cannot be achieved due to overlap of the target with an OAR, the target coverage can be compromised in order to meet the constraint.

<u>Treatment delivery:</u>

All treatments will be performed with high-precision image guided RT using a linear accelerator with ESTRO-ACROP specifications for SABR [Freislederer et al].

1. *Conventional radiotherapy:*

In the conventional RT group, image-guidance will consist of portal images or cone-beam CT showing the relevant bony anatomy.

2. *SABR*

In the SABR arm, a cone-beam CT will be performed for image guidance and positioning will be adapted using a 3 or 6 degrees of freedom treatment couch.

5.2 Allocation to treatment groups and blinding

This is a randomized controlled trial. Due to the type of intervention, blinding is not possible.

Randomization will be completed on a per patient basis (not lesion based) in a 1:1 ratio to the observational arm receiving systemic therapy / observation (Arm A) or to the arm receiving early RT plus systemic therapy / observation (Arm B). Randomization will be performed by the site staff in the window between screening and start of treatment using an electronic randomization tool in the eCRF that uses variable block randomization as randomization algorithm.

The following stratification factors are taken into consideration for randomization:

- NRF prognostic class (0-1 vs 2)
- high-risk disease location (spine location vs. other)
- bone modifying agents (yes vs. no).

Assignment of the subject identification number

At screening, each potential study participant will be assigned a subject identification number that will be retained as the primary identifier for the subject throughout their participation in the study. The subject-id consists of a sequential 6-digit number (comprised of a 2-digit study site number -11, 12, etc.- and a 4-digit number incremental per center representing the sequential order in which they are screened: 110001, 110002, etc.), so that each subject is numbered uniquely across the entire database. Upon signing the ICF, the subject is assigned to the next sequential subject-id available to the Investigator through the electronic data capture system.

5.3 Treatment compliance and adherence

After the RT session(s), RT parameters should be captured in the eCRF. The study site must maintain accurate records demonstrating dates and details of treatment interventions of all patients that have entered the study and capture these in the eCRF.

The following RT parameters are collected at the end of the RT treatment:

- radiation technique used
- date of the first and last RT session
- total dose delivered
- number of fractions delivered
- if early termination of RT, reason for this as well as fractions and dose that were originally planned
- GTV Volume: … cm^3

- PTV: V100% = ...%

Furthermore, at the end of the treatment period it will be documented in the eCRF whether the patient received observation or systemic therapy. In case systemic therapy was used, the following information will be recorded:

- Name of systemic therapy
- Start date systemic therapy
- Whether systemic therapy was interrupted for RT (and if applicable the duration of the interruption)

5.4 Prohibited or restricted medications/interventions

There are no prohibited medications.

All pain medication (including corticoid therapy), bone-modifying agents and anticancer therapy used within 7 days prior to the screening visit and through the end of the study will be recorded.

The decision for (dis)continuation of concomitant anticancer therapy with possible radiosensitizing effects is left at the discretion of the treating physician.

6. Study conduct

6.1 Study procedures

As noted in Section 3.1, participation in the HERMES study will comprise a screening period, where screening assessments must be completed. Eligible, consenting subjects will then undergo treatment with a post-treatment follow-up period to monitor safety and efficacy. The visit schedule and all study procedures and assessments are presented in the SOE in Table 1.

The results of all assessments and procedures will be documented in the subject's medical record and in study documentation, including the electronic case report form (eCRF), as applicable.

6.1.1 Screening period

Documentation of written informed consent (from the patient or his/her legally authorized representative) is required before any study specific procedure, including screening procedures, takes place.

Patients will be screened for eligibility (i.e. fulfilling inclusion/exclusion requirements) based on medical record, anamnestic and clinical information from the treating physician.

Screening will include the following evaluations:

- Demographic data (see section 7.1.2.)

- Medical history and prior medications (i.e. anticancer therapy, bone-modifying agents and pain medications (including corticoid therapy) taken within 7 days prior to screening) (see section 4.4.3. and section 7.1.1.).
- Determination of Karnofsky performance score (KPS) (see section 7.1.4 and appendix 5.)
- Pain assessment (NRS score; see section 7.1.3. and appendix 1)
- Determination of high-risk metastase(s) characteristics (see section 7.1.5.)
- Quality of life questionnaires (see section 7.1.6. and section 7.4)
- Pregnancy test in case of premenopausal women (see section 7.1.7. and section 4.4.1.)
- Reporting of adverse events that are related to the bone metastatic disease or related to the radiotherapy (only for patient in arm B) as measured with NCI-CTCAE v5.0 (see appendix 4)

More details regarding screening assessments can be found in section 7.1. Once all screening procedures are completed, eligibility will be determined according to the inclusion/exclusion criteria as detailed in section 4. The review of eligibility criteria must be captured in the eCRF.

6.1.2 Treatment planning and treatment period

Upon enrollment in the study, patients will be randomized into either the observational arm receiving observation / systemic therapy (arm A) or the upfront RT arm receiving upfront RT plus systemic therapy / observation (arm B).

For patients randomized in arm B, radiotherapy will start within 21 days after the date of randomization. Treatment planning and delivery is described in section 5.1.

Any toxicity (graded according to CTCAE v5.0) that occurs during this period should be entered in the database. AE that took place during this treatment period will be documented at the first follow-up visit.

6.1.3. Follow-up period

During on site follow-up visits at 1 month (+/-1 week), 3 months (+/- 3 weeks), 6 months (+/- 3 weeks), 12 months (+/- 3 weeks), 18 months (+/- 3 weeks) and 24 months (+/- 3 weeks) after date of randomization, the following assessments will take place:

- Determination of Karnofsky performance score (KPS) (see appendix 5)
- EQ-5D-5L QoL and QLQ-C15-PAL questionnaire (see appendix 2, appendix 3 and section 7.4)
- Acute and late toxicity assessment: as measured with NCI-CTCAE v5.0 (see appendix 4)
- Concomitant medications: pain medication (including corticoid therapy), bone-modifying agents and anticancer therapy (see section 4.4.3.)
- Survival data (survival status, date of death, primary cause of death)

Follow-up imaging will not occur standardized but is left at the discretion of the treating physicians (i.e. is part of the standard of care).

6.2 End of study

The end of the study is defined as the date when the last follow-up visit takes place (i.e. 24 months after date of randomization of the last participant if his/her participation was not discontinued early)

In case an SSE occurs, the assessments that should take place during the next follow-up visit, should be completed at that time point, preferentially within one week. These assessments must be documented in the eCRF. Furthermore, the type of SSE (e.g. symptomatic pathological fracture,…) needs to be registered. In case of fracture or compression, the location and planned treatment must also be documented. In case of RT or surgery, the location and reason must be registered. Afterwards, only survival data and possible occurrence of another SSE will be recorded on the planned FU visits until 24m after the randomization date.

6.3 Discontinuation or withdrawal

List the procedures that will be performed for each subject that withdraws prior to completing the study.

6.3.1 Criteria for withdrawal from the study

In accordance with applicable regulations, a subject has the right to withdraw from the study, at any time and for any reason, without prejudice to their future medical care.

If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Subject data will be included in the analysis up to the date of the withdrawal of consent.

Apart from withdrawal of consent, reasons for early termination of individual subjects may include:

- Protocol deviations or subject non-compliance (must be specified on the appropriate CRF)
- Adverse events
- The Investigator considers that it is in the subject's best interest to discontinue their participation in the study
- Subject is lost to follow-up
- Other (must be specified)

In case of discontinuation without withdrawal of informed consent, survival data will be collected at the remaining follow-up timepoints (i.e. 1m +/- 1 week, 3m +/- 3 weeks , 6m +/- 3 weeks, 12m +/- 3 weeks, 18m +/- 3 weeks and 24m +/- 3 weeks after randomization date) and the occurrence of an SSE will be registered in the eCRF if it occurs within 24m after the randomization date.

If a subject is withdrawn because of an AE, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all serious adverse events (SAE) considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

6.3.2 Subjects lost to follow-up

A subject will be considered lost to follow-up if they fail to return for scheduled visits and are unable to be contacted by the study center.

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

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible. The study center must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or equivalent methods). These contact attempts should be documented in the subject's CRF.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study.

6.4 Study termination

The sponsor reserves the right to terminate any portion of the study at any time. Possible reasons for termination include:

1. Safety reasons.
2. New scientific knowledge becomes known that makes the objectives of the study no longer feasible/valid.
3. Unsatisfactory enrollment of participants.

In terminating the study, the sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

7. Study assessments

The frequency and timing of efficacy, safety, and other measurements for subjects are presented in the Schedule of Events (SOE) (see Table 1).

7.1 Screening evaluations and measurements

Within 3 weeks prior to randomization:

7.1.1 Medical History and Prior Medications

-Medical history (including date of the initial diagnosis of the primary cancer, site and histology of the primary cancer, date of diagnosis of metastatic disease and the number of metastases at the time of the screening visit)

-Anticancer therapy, bone-modifying agents and pain medications (including corticoid therapy) within 7 days before screening visit will be recorded at screening.

7.1.2 Demographics

Gender, year of birth and age will be recorded as part of the screening procedures.

7.1.3 Pain assessment

As the presence of asymptomatic or minimally symptomatic high-risk bone metastase(s) is an inclusion criterion of this study, the patient's pain will be evaluated per lesion by determining the Numeric Pain Rating Scale (NRS) score. Asymptomatic or minimally symptomatic is defined as an NRS score ≤2. The NRS score is explained in appendix 1 of this protocol.

7.1.4 Karnofsky Performance Score (KPS)

The KPS should be documented in the subject's medical record or study source documentation at applicable visits. A copy of the document is included in Appendix 5 (Karnofsky Performance Score Assessment) for reference.

7.1.5 High-risk bone metastase(s) characteristics: (localization, high-risk definition, number of metastases enrolled)

Based on imaging (CT, MRI or PET-CT), the characteristics of the high-risk bone metastasis(es) that is (are) asymptomatic or minimally symptomatic will be determined and captured in the eCRF, including the total number of bone metastases, the location of the high-risk bone metastases (high-risk definition) and the number of metastases enrolled.

High-risk is defined as follows:

- Bulky site of disease in bone (diameter ≥ 2 cm)
- Disease involving the hip (acetabulum, femoral head, femoral neck), shoulder (acromion, glenoid, humeral head), or sacroiliac joints
- Disease in long bones with cortical involvement of >1/3 in proportion to the diameter of the bone
  (humerus, radius, ulna, clavicle, femur, tibia, fibula, metacarpals, phalanges)
- Disease in vertebrae of the junctional spine (C1-2, C7- T1, T12-L1, L5-S1) and/or disease with posterior element involvement or epidural extension (Bilsky epidural compression score 1a-3; see appendix 7) [Bilsky et al]

Furthermore, whether metastases on other locations than the bone are present should be documented in the eCRF.

Images up to 12 weeks old at the time of randomization are allowed. If not available, screening will take place at the time repeat imaging will be performed according to the standard of care guidelines.

7.1.6 QLQ-C15-PAL questionnaire and EQ-5D-5L questionnaires

The EORTC QLQ-C15 questionnaire and the EQ-D5-5L questionnaire are used to evaluate the quality of life of the patients in both treatment arms (see section 7.4.).

7.1.7 Pregnancy test for women of child-bearing potential

Pregnancy testing (serum HCG) should be conducted at screening (within 72 hours before the randomization date) for women of child-bearing potential. Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the patient's participation in the study.

7.1.8. Number of Risk Factors (NRF) score

The NRF score should be documented in the subject's medical record or study source documentation during screening (see section 5.1) as it will be used to determine the RT scheme (palliative vs stereotactic dose). In addition, NRF score should be documented in the eCRF.

7.1.9. Assessment of (serious) adverse events ((S)AE) during screening

The occurrence of (S)AE as measured with NCI-CTCAE v5.0 (see appendix 4) will be documented in the eCRF (see section 8). Only (S)AE that are related to the bone metastatic disease will be documented at screening.

7.2 Efficacy Evaluations

- Comparison of the number of SSE's in both study arms. SSEs are defined as:
    - symptomatic pathological fracture
    - spinal cord compression leading to neurological deficit or pain
    - Indication for palliative radiotherapy (for bone pain, cord compression or (impending) fracture)
    - Indication for orthopedic surgery (for bone pain, cord compression or (impending) fracture)

All SSE's will be recorded in both study arms. Patiens in the upfront RT arm may develop an SSE in a bone metastasis that was not previously included in the study, which also needs to be registered. An exception are SSE's in bone metastases that were already treated with surgery or RT before study participation

Patients in the upfront RT arm developing new minimally symptomatic or asymptomatic high-risk bone metastases during study participation are strongly advised to further be treated with preventive RT. Details concerning the characteristics of these new high-risk metastases as well as details regarding the preventive RT must be captured in the eCRF.

- Comparison of the number of **hospitalizations** related to the high-risk bone metastasis(es) between observation/systemic therapy and upfront RT plus observation/systemic therapy
- **Overall survival:** from time of study randomization to date of death of any cause or last follow-up visit (24m after randomization date)
- To compare **quality of life** between observational arm (arm A) and upfront RT arm (arm B), using the EORTC QLQ-C15-PAL form and the EuroQol Group EQ-5D-5L form

7.3 Safety Evaluation

Acute or late toxicity will be assessed and scored using CTCAE version 5.0 and recorded in the eCRF. More specifically, subjects will be questioned at each follow-up visit regarding AE and they will be instructed to inform the investigator or study personnel of any AE occurring at any time during the trial.

Moreover, the patient's Karnofsky performance score will be evaluated during every follow-up visit.

7.4 Patient reported outcome

The patient will report on his quality of life (QoL) by completing the EORTC QLQ-C15-PAL and the EuroQol Group EQ-5D-5L questionnaires in Dutch, English or French depending on the native language of the patient (see appendix 2 and appendix 3). These questionnaires will preferentially be completed digitally, but will also be available on paper.

All patient reported outcome (PRO) assessments should be completed before any other tests, procedures, or other consultations, to prevent influencing participant perceptions. Relevant actual dates and times of assessments will be recorded in the source documentation and eCRF.

8. Safety management and reporting

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

8.1 Definitions and criteria

8.1.1 Definition of an adverse event (AE)

An AE is any untoward medical occurrence in a subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

8.1.2 Definition of a serious adverse event (SAE)

An SAE is defined as any untoward medical occurrence that, at any dose:

- results in death
- is life-threatening
  The term 'life-threatening' in the definition of "serious" refers to an event in which the subject 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.
- requires in-patient hospitalization or prolongation of existing hospitalization
  In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- results in persistent or significant disability/incapability
  The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- is a congenital anomaly or birth defect
- is medically important
  Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  Examples of such medical events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.3 Severity or intensity criteria

AE are to be recorded on the eCRF. Severity will be graded according to the CTCAE v 5.0, published November 27, 2017 (CTCAE v5.0 – see Appendix 4).

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1**: Mild; an event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Grade 2**: Moderate; an event that causes sufficient discomfort and interferes with normal everyday activities.

- **Grade 3**: Severe; an event that prevents normal everyday activities.
- Note: An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death related to AE.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

8.1.4 Causal relationship of an AE/SAE to the intervention

The Investigator is obligated, and will use clinical judgement, to assess the relationship between study treatment and each occurrence of each AE/SAE. Furthermore, the investigator will assess the relationship between the bone metastatic disease and each occurrence of each AE/SAE. Only AE/SAE that are related to the bone metastatic disease or related to radiotherapy (only applicable for patients in arm B) will be reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (see appendix 4). The relationship of each AE/SAE to the study intervention should be characterized using one of the following: related to RT, related to bone metastatic disease or unrelated.

Table 3 Adverse event causal relationship with study treatment

Related to RT (only applicable for patients in arm B)	There is a reasonable possibility that the RT is the cause of the AE.
Related to bone metastatic disease	There is a reasonable possibility that the bone metastatic disease is the cause of the AE.
Unrelated	There is no reasonable possibility that the RT or the bone metastatic disease is the cause of the AE.

8.1.5 Expectedness of an SAE:

The following definitions are general guidelines to help assign grade of attribution:

Adverse reaction (AR): any AE caused by a study treatment.

Suspected adverse reaction (SAR): any AE for which there is a reasonable possibility that the study treatment caused the AE.

Unexpected: an event is considered unexpected if its nature or severity is not consistent with a recognized side-effect of the study treatment.

8.1.6 Outcome

Outcome of an AE or SAE will be recorded on the AE eCRF as follows:

- Recovered/resolved
- Recovering/resolving

- Recovered/resolved with sequalae
- Not recovered/not resolving
- Fatal
- Unknown

8.2 Reporting procedures

8.2.1 Method of detecting (S)AE

AE will be reported by the subject. Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. For each SAE, it should be evaluated whether it concerns an SSE. If it concerns an SSE, the SAE should be documented as such in the eCRF and the necessary actions should be taken (see section 6.2). In case hospitalization occurs, it should be evaluated whether the hospitalization is related to the high-risk bone metastasis(es) and this information should be documented in the eCRF.

8.2.2 Period for collecting AE and SAE information

During the period from main ICF signing to the last follow-up visit (24m after randomization date), date of death of any cause or early end of participation in the study due to other reasons, all (S)AE that are related to the bone metastatic disease or related to radiotherapy (only applicable for patients in arm B) will be documented in both study arms.

The following applies for (S)AE related to RT (arm B):

Toxicity that appears within 90 days after the last RT dose will be regarded as acute toxicity.

Toxicity that appears >90 days after the last RT dose administration will be regarded as late toxicity.

8.2.3 Investigator reporting of an (S)AE to the sponsor

When an AE/ SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/ SAE information in the eCRF. Each event must be recorded separately.

There may be instances when copies of medical records for certain cases are requested by. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/ SAE.

The investigator shall report all serious adverse events immediately (<24h), after first knowledge, to the sponsor. Information regarding SAE will be transmitted to the sponsor using the SAE form, which must be completed and signed by a physician from the study site and transmitted to the sponsor (gza.safetycto@zas.be) within 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

All SAE that have not resolved by the end of the study or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value/status is available
- the event can be attributed to agents other than the treatment or to factors unrelated to study conduct
- it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The immediate and follow-up SAE reports shall identify subjects by patient specific study numbers.

The following situations do not need to be reported as SAE:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by the treatment;
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated;
- Social and/or convenience admission to a hospital;
- Medical or surgical procedure, e.g., endoscopy, appendectomy; unless the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an AE);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.2.4 Notification of an SAE to the Ethical Committee

The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent ethics committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected unexpected serious adverse reactions shall be reported to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. The sponsor shall also inform the other investigators.

Once a year throughout the experiment, the sponsor shall provide the ethics committee with an annual safety report, listing all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety (development safety update report). Regarding those adverse events and serious adverse reactions the investigator will take all reasonable measures, in consultation with sponsor, to protect subjects at risk following the occurrence of such events.

8.2.5 Clinical Laboratory Findings

Clinical laboratory findings are not applicable for the HERMES study.

9. Statistical considerations

9.1 Justification of sample size

In collaboration with statistical experts UGent a sample size calculation was performed. A hazard ratio of 0.5 is deemed clinically relevant, increasing the estimated 2-year SSE free survival from 20% to 45%. Assuming exponentially distributed SSE-free survival, setting alpha to 0.05 and the required power to 0.8 and assumed non-informative drop out to 20%, this results in a sample size of 120 (96 without drop out) with a required number of events of 65.

Hazard ratio (HR) = 0.5 is in between previously observed effect sizes in similar settings: Different trials analyzing the use of bone modifying agents with the presence of SREs, showing a HR around 0.7 [Smith et al; O'Carrigan et al; Rosen et al)]. In the above-mentioned phase II trial [Rosen et al] there was a large reduction in SREs from incidence from 29% to 1.6% at 1 year in the RT group. Because in our trial SSEs and not SREs will be analyzed, we expect a more conservative HR. This was also demonstrated in a trial comparing skeletal-related events with symptomatic skeletal events for two different bone modifying agents [Smith et al].

A sample size of 96 patients was calculated to have an 80% power and an alpha< 0.05. With an estimated dropout of 20%, the **total sample size will be 120** with a required number of events of 65.

Each patient will be stratified by their prognostic class (0-1 vs 2), high-risk disease location (spine location vs. other) and bone modifying agents (yes vs. no) in this hierarchical order. With 3 stratification factors for randomization, there are 8 strata, which is rather high for only 60 patients per arm. Strata where only 1 arm is present and the events in these strata, are implicitly ignored in the estimation/testing. Strata with less then 10 patients will be merged with the corresponding stratum with the same value for factor A and B, but different value for C in the upfront decided hierarchical order (cfr above).

Randomization will be completed on a per patient basis (not lesion based), even though each patient may have up to 5 multiple sites of metastatic bony disease.

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9.2 Population description

Patients suffering from asymptomatic or minimally symptomatic high-risk bone metastases will be screened for inclusion in this HERMES study. Data will be analyzed in accordance with the subjects' randomized treatment assignment.

9.3 Statistical methods for analysing primary and secondary outcomes

Primary objective:

The primary endpoint (SSE-free survival) is a composite endpoint of SSEs and death (death before SSE is part of the endpoint, not a competing risk). The primary endpoint is time until the occurrence of SSE in any bone metastasis or death from the date of randomization whichever occurs first. Data suggest that the median SSE-free survival is around 10.4 months. With a HR of 0.5, we hypothesize that the median SSE-free survival will be 20.8 months.

A proportion of patients will have multiple high-risk bone lesions. Pain will be reported lesion-based, however the SSE-free survival remains patient-based as this is more clinically relevant.

Secondary objectives

- The number of **hospitalizations** related to the high-risk metastase(s) will be compared between systemic therapy / observation (arm A) and upfront RT plus systemic therapy / observation (arm B) from date of study randomization to last follow-up visit (24m after randomization date), date of death of any cause or early end of participation in the study due to other reasons
- **Overall survival** will be assessed from time of study randomization to date of death of any cause or last follow-up visit (24m after randomization date)
- **Quality of life** will be compared between systemic therapy / observation (arm A) and upfront RT plus systemic therapy / observation (arm B), using the EORTC QLQ-C15-PAL questionnaire (see appendix 2) and the EuroQol Group EQ-5D-5L questionnaire (see appendix 3)
- **Adverse events** in both study arms will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (see appendix 4) from the time of ICF signing to last follow-up visit (24m after randomization date), date of death of any cause or early end of participation in the study due to other reasons. Only adverse events that are related to the bone metastatic disease or related to the radiotherapy (only for patients in arm B) will be reported in the eCRF.

9.4 Interim analyses

After 2 years, a blinded interim analysis is planned to estimate the event rate by our statistical expert team. Depending on the result, additional patients can be recruited or the FU for the patients still in the trial can be extended. As this is a blinded interim analysis, no alpha-adjustment is required.

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10.Study management

10.1 Regulatory and ethical considerations

10.1.1 Regulations and guidelines

The investigator is responsible for ensuring that the study is performed in compliance with this protocol, the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the current IHC guidelines on Good Clinical Practice (GCP) and all of the applicable regulatory requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

10.1.2 Independent Ethics Committees (IEC)

The protocol, protocol amendments, ICF, participant information sheets and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study centre and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study centre at which the Investigator has not signed the protocol.

10.1.3 Insurance and indemnification

The Sponsor will ensure sufficient insurance is available to enable them to indemnify and hold the Investigator's and relevant staff as well as any hospital, Institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the investigational therapy but only to the extent that the claim is not caused by the fault or negligence of the patients or investigators. An insurance certificate will be supplied to the involved parties, including the Investigator (s).

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The Sponsor has taken a no fault insurance for this study, in accordance with the relevant legislation (article 29, Belgian Law of May 7, 2004):

- Sponsor: Ziekenhuis aan de Stroom vzw – Kempenstraat 100 – 2030 Antwerpen
- Insurance details*:* MS Amlin Insurance SE - Koning Albert II-laan 37 - B-1030 Brussel

10.1.4 Benefit-risk assessment

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH, GCP, and applicable regulatory guidelines.

To further minimize any potential risk, careful monitoring of each subject will be conducted throughout the study to detect any adverse events (AE) or safety signals, as delineated in the schedule of events.

Potential risks of study participation

The intervention in this study is early, upfront radiation therapy to asymptomatic or minimally symptomatic bone metastases.

In general, a single fraction of 8 Gy will be prescribed according to general recommendations for patients with painful bone metastases. This single day treatment is characterized by its **limited patient burden.** Radiation dose and planning will follow international guidelines and will be delivered with contemporary radiation techniques, thereby **minimizing the side effects for** patients [Oldenburger et al, Nguyen et al, Lutz et al].

Potential benefits of study participation

The aim of this trial is reducing the number of SSEs, inherently a **symptom-based endpoint.** Therefore, the hypothesis of the project is to decrease symptoms and side effects for each individual patient.

Risk-benefit assessment

According to the ESTRO-ACROP recommendations, the majority of patients experience no or mild acute toxicity after conventional radiotherapy, the possibility of experiencing side effects should not be a reason to withhold patients with bone metastases from this treatment. No high-grade side effects are expected.

Patients in the observational arm will not receive RT but have the possibility to receive palliative RT to progressed, painful lesions (an SSE) only at the time of symptom worsening.

10.2 Informed consent

For each study participant, informed consent will be obtained in writing before any protocol-related activities commence. As part of this procedure, the investigator or a designated representative must explain orally and in writing, by means of the ICF, the nature, duration, the purpose of the study, the number of visits, the assessments, procedures to undergo, and the action of the treatment in such a manner that the participant is aware of the potential risks, inconveniences, or adverse effects that may occur. Participants should be informed that they may withdraw from the study at any time without any resulting disadvantage and prejudice to their standard treatment care. They will receive all information that is required by national regulations and current ICH and GCP guidelines.

The participant and the investigator will sign the ICF. A copy will be provided to the participant. The originally signed ICF will remain at the study center. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

All participants will be insured against injury caused by their participation in the study according to the legal requirements. They will be informed about the insurance and the resulting obligations on their part.

10.3 Subject identification, enrollment and screening logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification number and year of birth.

10.4 Quality control and assurance

The sponsor will implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of the study with a focus on study activities essential to ensuring protection of participants and the reliability of study results. The quality management system will use a risk-based approach.

10.4.1 Data monitoring

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised study centre 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.

The Medical Monitor will act as the main point of contact for PIs and sites to assess subject eligibility and ongoing protocol/safety management issues.

The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (e.g., hospital medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

10.4.2 Audits

The study may be audited by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required participant records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.4.3 Protocol amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly documented and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to a trial participant(s). In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

10.4.4 Protocol deviations

All protocol deviations will be assessed and documented on a case-by-case basis before database lock. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the study, non-compliance, participant management, or participant assessment should be described. Protocol deviations will be listed, and significant protocol deviations will be reported to the Ethics Committees (EC).

10.4.5 Records

10.4.5.1 Data capture and management

Study data will be recorded on eCRF (electronic case report forms) with regular back up and controls for further analyses. Study investigators and authorized study staff will be authorized for the eCRF, and will be identifiable by login.

10.4.5.2 Source documentation

Source documentation will include the demographic data, visit dates, signed ICF, and study number relating to the eCRF, and will be found in the oncology and radiotherapy departments participating to the study.

10.4.5.3 (Electronic) care report forms

The investigator should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the center's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

All clinical data will be captured via electronic data capture. The investigator's study center staff will enter and edit the data via a secure network. Electronic CRFs will be used for all participants. The investigator's data will be accessible from the investigator's site throughout the study. The eCRF must be kept current to reflect participant status at each part during the course of the study. The eCRF will not capture personalized data. The investigator must make a separate confidential record of personalized details (name and initials) on the participant identification and enrollment log. All changes to data are done by the investigator or designated site personnel through the electronic data capture system.

It is the responsibility of the principal investigator of the study center to ensure that all participant discontinuations or changes in treatment entered on the participant's eCRF are also made on the participant's medical records. The eCRFs for any participant leaving the study should be completed at the time of the final visit or shortly thereafter.

10.4.5.4 Confidentiality and data protection

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 30 July 2018 and 22 Aug. 2002].

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, ethics committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

10.4.5.5 Record retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). All essential documents will be retained according to ICH GCP for a minimum of 25 years after study termination and in compliance with all applicable legal and regulatory requirements.

The investigator/institution will take measures to prevent accidental or premature destruction of these documents. If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.5 Study termination or study site closure

The Sponsor, Investigator and the IEC/ IRB reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the CRFs. The Investigator should notify the relevant IEC/ IRB in writing of the study's completion or early discontinuation.

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 IRB/ IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

11. Clinical study report

A CSR will be prepared in accordance with ICH Guidance E3.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report

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will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

The full CSR, or where required the CSR synopsis, will be submitted to the IEC within 12 months from the end date of the study.

12.Use of information and publication

Results from the study will be submitted for publication in high-ranking journals in the field of radiotherapy and/or oncology.

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14.Appendices

Appendix 1: Numeric Pain Rating Scale (NRS)

During screening, the patient needs to report for each lesion his/her pain by indicating the intensity of pain on average during the past week (i.e. 7 days) on a scale from zero (i.e. no pain at all) up to 10 (most imaginable pain).

Numeric Pain Rating Scale

Selecteer het cijfer dat het best de ernst van uw pijn weergeeft.
Hoe hevig was uw pijn (gemiddeld) de afgelopen week (7 dagen)?

0	1	2	3	4	5	6	7	8	9	10
geen enkele pijn										**meest voorstelbare pijn**

Appendix 2: EORTC QLQ-C15-PAL

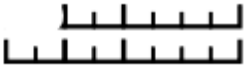
Questionnaire will be used in Dutch, English and French.

DUTCH

EORTC QLQ-C15-PAL (versie 1)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is? Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Patiëntcode

De datum van vandaag (Dag, Maand, Jaar): 

	Helemaal niet	Een beetje	Nogal	Heel erg
1. Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
2. Moet u overdag in bed of op een stoel blijven?	1	2	3	4
3. Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:	Helemaal niet	Een beetje	Nogal	Heel erg
4. Was u kortademig?	1	2	3	4
5. Heeft u pijn gehad?	1	2	3	4
6. Heeft u moeite met slapen gehad?	1	2	3	4
7. Heeft u zich slap gevoeld?	1	2	3	4
8. Heeft u gebrek aan eetlust gehad?	1	2	3	4
9. Heeft u zich misselijk gevoeld?	1	2	3	4

Wilt u a.u.b. naar de volgende bladzijde gaan.

Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
10. Had u last van obstipatie? (was u verstopt?)	1	2	3	4
11. Was u moe?	1	2	3	4
12. Heeft pijn u gehinderd bij uw dagelijkse bezigheden?	1	2	3	4
13. Voelde u zich gespannen?	1	2	3	4
14. Voelde u zich neerslachtig?	1	2	3	4

Wilt u voor de volgende vraag het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is?

15. Hoe zou u uw algehele "kwaliteit van het leven" gedurende de afgelopen week beoordelen?

1	2	3	4	5	6	7
Erg slecht						Uitstekend

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Appendix 3: EuroQol Group EQ-5D-5L questionnaire

Questionnaire will be used in Dutch, English and French.

Gezondheidsvragenlijst

Vlaamse versie voor België

(Flemish version for Belgium)

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Vink onder elke titel het ENE vakje aan dat het best uw gezondheid VANDAAG beschrijft.

MOBILITEIT

- Ik heb geen problemen met rondwandelen ❑
- Ik heb een beetje problemen met rondwandelen ❑
- Ik heb matige problemen met rondwandelen ❑
- Ik heb ernstige problemen met rondwandelen ❑
- Ik ben niet in staat om rond te wandelen ❑

ZELFZORG

- Ik heb geen problemen met mijzelf te wassen of aan te kleden ❑
- Ik heb een beetje problemen met mijzelf te wassen of aan te kleden ❑
- Ik heb matige problemen met mijzelf te wassen of aan te kleden ❑
- Ik heb ernstige problemen met mijzelf te wassen of aan te kleden ❑
- Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

- Ik heb geen problemen met mijn dagelijkse activiteiten ❑
- Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
- Ik heb matige problemen met mijn dagelijkse activiteiten ❑
- Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
- Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN / ONGEMAK

- Ik heb geen pijn of ongemak ❑
- Ik heb een beetje pijn of ongemak ❑
- Ik heb matige pijn of ongemak ❑
- Ik heb ernstige pijn of ongemak ❑
- Ik heb extreme pijn of ongemak ❑

ANGST / DEPRESSIE

- Ik ben niet angstig of depressief ❑
- Ik ben een beetje angstig of depressief ❑
- Ik ben matig angstig of depressief ❑
- Ik ben erg angstig of depressief ❑
- Ik ben extreem angstig of depressief ❑

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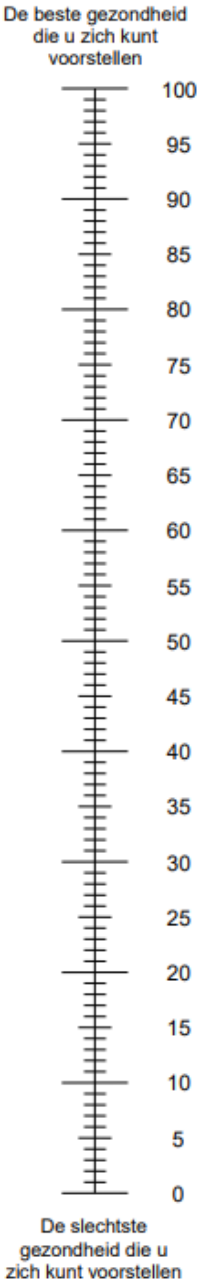
- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal (te vergelijken met een thermometer) is genummerd van 0 tot 100.
- 100 staat voor de beste gezondheid die u zich kunt voorstellen.
  0 staat voor de slechtste gezondheid die u zich kunt voorstellen.
- Plaats een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer nu het getal dat u aangeduid hebt op de meetschaal in het onderstaande vakje.

UW GEZONDHEID VANDAAG = ☐



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Appendix 4: National Cancer Institute Common Terminologie Criteria for Adverse Events (NCI-CTCAE)

The Cancer Therapy Evaluation Program NCI-CTCAE version 5.0 (November 27, 2017) is presented at the NCI website, accessible via the following link:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

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Appendix 5: Karnofsky Performance score assessment [Crooks et al]

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%)

CRITERIA

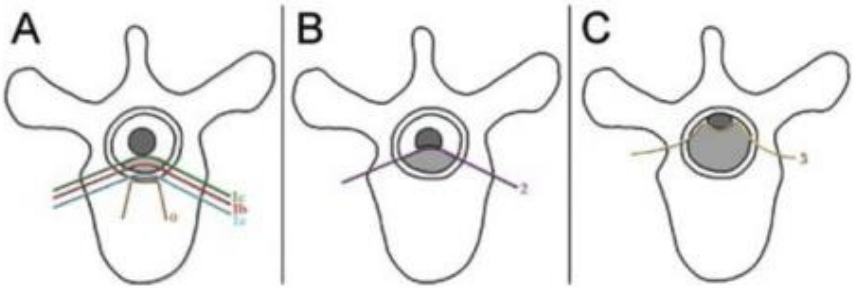
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 6: Spinal instability neoplastic score (SINS) [*Fourney et al*]

SINS Component	Score
Location	
• Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
• Mobile spine (C3-C6, L2-L4)	2
• Semirigid (T3-T10)	1
• Rigid (S2-S5)	0
Pain*	
• Yes	3
• Occasional pain but not mechanical	1
• Pain-free lesion	0
Bone lesion	
• Lytic	2
• Mixed (lytic/blastic)	1
• Blastic	0
Radiographic spinal alignment	
• Subluxation/translation present	4
• De novo deformity (kyphosis/scoliosis)	2
• Normal alignment	0
Spinal body collapse	
• > 50% collapse	3
• < 50% collapse	2
• No collapse with > 50% body involved	1
• None of the above	0
Posterolateral involvement of spinal elements†	
• Bilateral	3
• Unilateral	1
• None of the above	0

*Pain improvement with recumbency and/or pain with movement/loading of spine.
†Facet, pedicle, or costospinal joint fracture or replacement with tumour.

Appendix 7: ESCC grading score [Bilsky et al]



Schematic representation of the 6-point ESCC grading scale.

Grade 0: bone-only disease;

Grade 1a: epidural impingement, without deformation of the thecal sac;

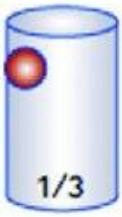
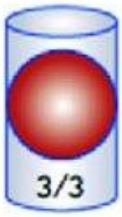
Grade 1b: deformation of the thecal sac, without spinal cord abutment;

Grade 1c: deformation of the thecal sac with spinal cord abutment, but without cord compression;

Grade 2: spinal cord compression, but with cerebrospinal fluid (CSF) visible around the cord;

Grade 3: spinal cord compression, no CSF visible around the cord.

Appendix 8: Mirels score [Mirels et al]

Fracture		Score
Site	Upper limb	1
	Lower limb	2
	Proximal femur (peri-trochanteric)	3
Pain	Mild	1
	Moderate	2
	Functional (worse on use of limb)	3
	Sclerotic (blastic, gain of bone)	1
Lesion	Mixed (combination of sclerotic and lytic)	2
	Lytic (loss of bone)	3
Ratio of lesion to diameter of bone*	<1/3 diameter 1 	
	1/3-2/3 2 	
	>2/3 diameter 3 	
Total	8=15% fracture risk	/12
	9=33% fracture risk	

*Permeative or "moth-eaten" lesions can be poorly defined, multiple in nature, or ragged in appearance, and can be difficult to accurately quantify using this system.31 Seek specialist radiology or orthopaedic input for aid in classifying lesions if required

- Score ≤ 7 = the probability of fracture (5%) is low and such a lesion may be treated conservatively
- Score 8 = the probability of fracture (15%) is intermediate, discussion with orthophedic surgeon is advised
- Score ≥9 = the probability of fracture (33% and more) warrants prophylactic fixation of the bone