**STUDY SYNOPSIS**

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| **Protocol title:** | A phase III randomized-controlled, single-blind trial to improve quality of life with stereotactic body radiotherapy for patients with painful bone metastases |
| **Short title/acronym:** | ROBOMET |
| **Protocol number:** | CTOR18072GZA |
| **BUN:** | B099201838350 |
| **Sponsor:** | GZA vzw<br>Oosterveldlaan 22, 2610 Wilrijk, Belgium |
| **Study responsible physician:** | Dr. Piet Dirix<br>Radiation Oncology, Oncologisch Centrum GZA<br>Phone: +32(0)34433737, Fax: +32(0)4433009<br>piet.dirix@gza.be |
| **Investigator(s)/study center(s):** | Dr. Piet Dirix, GZA<br>Dr. Piet Ost, UZ Gent |
| **Study objectives and endpoints:** | **Primary objective**<br>To double the complete response rate of antalgic radiotherapy for symptomatic bone metastases while at the same time decreasing acute toxicity through the use of stereotactic body radiotherapy, delivering a single fraction dose of 20.0 Gy with high precision.<br><br>**Primary endpoint**<br>Pain response at the treated index site 30 days after RT.<br><br>**Secondary objectives**<br>- To compare pain flare at 24-48-72 hours after radiotherapy.<br>- To compare the duration of pain response.<br>- To compare re-irradiation need.<br>- To asses acute toxicity in both arms.<br>- To asses late toxicity in both arms.<br>- To assess quality of life in both arms.<br>- To assess subsequent symptomatic skeletal events.<br><br>**Secondary endpoints**<br>1. **Pain flare** at 24-48-72 hours after radiotherapy, defined as an increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline [14]. For calculation of OMED, the conversion tool provided in Attachment 2 can be used.<br>2. **Duration of pain response**, i.e. time until pain progression (defined as an increase in pain score of 2 or more above baseline at the treated site with stable OMED, or an increase of 25% or more in OMED compared with baseline with the pain score stable or 1 point above baseline) [14].<br>3. **Re-irradiation need.**<br>4. **Acute toxicity,** as measured with CTCAE version 5.0 (Attachment 3) |



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| | 5. **Late toxicity,** as measured with CTCAE version 5.0 (Attachment 3)<br>6. **Quality of life** according to the EORTC QLQ-C30 & BM22 questionnaires [15], see Attachments 4 and 5.<br>7. Subsequent **SSE**, defined as symptomatic pathologic fractures, radiation or surgery to bone, and spinal cord compression. |
| **Study design:** | Randomized, single-blinded, phase III |
| **Planned sample size:** | 126 |
| **Medical condition under investigation** | Cancer patients with painful bone metastases who are referred for palliative, antalgic single-fraction radiotherapy |
| **Participant selection criteria:** | Each potential subject must satisfy all of the following criteria to be enrolled in the study:<br>1. ≥ 18 years old.<br>2. Histologically confirmed malignancy.<br>3. Pain score ≥ 2 on a scale from 0 to 10 (measured as the worst pain for the previous 3 days at the index site). If analgic dosing adjust ent is done less than 1 week before initiation of irradiation, a run-in period is recommended to minimize the risk that the analgesic effects will confound the measurement of the RT effects [14].<br>4. Radiological or (bone) scintigraphic evidence of bone metastasis at the site of pain.<br>5. Per lesion no more than 3 consecutive spine segments involved with one unaffected vertebral body above and below.<br>6. No more than 3 painful lesions needing treatment.<br>7. Life expectancy estimated at > 3 months.<br>8. Patients who have received the information sheet and signed the informed consent form.<br>9. Patients must be willing to comply with scheduled visits, treatment plan, and other study procedures.<br><br>Each potential subject must NOT satisfy any of the following criteria to be enrolled in the study:<br>1. Myeloma.<br>2. Bone metastasis in previously irradiated sites.<br>3. Previous radioisotope treatment for bone metastases within 30 days of randomization.<br>4. Complicated bone metastasis, i.e. impending and/or existing pathological fracture, spinal cord compression or cauda equina compression. A Spine Instability Neoplastic Score of ≥13 is considered unstable (see Attachment 10) ; a Bilsky-grade of ≥1a is considered impending or existing spinal cord compression; for femoral lesions, an unstable lesion is defined as >3 cm axial cortical involvement and/or circumferential cortical involvement >50% (see Attachment 11). |



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| | 5. Patients with significantly altered mental status or with psychological, familial, sociological or geographical condition potential hampering compliance with the study.<br>6. Individual deprived of liberty or placed under guardianship. |
| **Treatment:** | Standard treatment: RT with a single fraction dose of 8.0 Gy to the metastasis.<br>Experimental arm: SBRT with a single fraction dose of 20 Gy to the metastasis. |
| **Safety/tolerability:** | Rate of AE including SAE, AEs and CTCAE grade |
| **Trial registration:** | This study is registered on ClinicalTrials.gov with Identifier: NCT03831243 |

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