Synopsis

Title	Dose-intensified Image-Guided Fractionated Stereotactic Body Radiation Therapy for Painful Spinal Metastases versus Conventional Radiation Therapy: a Randomised Controlled Trial (DOSIS RCT)
Short title	DOSIS RCT
Sponsor / Sponsor-Investigator	Professor Doctor Matthias Guckenberger
Protocol version and date	Version 4.0; 11/12/2020
Trial registration	www.clinicaltrials.gov: NCT02800551 www.kofam.ch/de/studienportal: SNCTP000002145
Study category and rationale	*Type:* Clinical trial. *Subtype and Category:* Clinical trials with interventions that are neither a therapeutic product nor a transplant product, nor a transplant, Category A. *Rationale for the risk category:* Radiation therapy of the spinal metastases is indicated for the trial population regardless of their participation in the trial. Stereotactic body radiation therapy (SBRT) is a currently used and established treatment for painful spinal metastases. The interventions under investigation therefore involve no more than minimal additional risks and stress for the participating patients.
Study background and rationale	Radiation therapy is an effective palliative treatment for painful spinal metastases. Because metastatic disease is considered incurable and uncontrollable, palliation - pain relief, stability of the vertebra and stabilisation/improvement in neurological functions – is the primary treatment goal. Recent improvements in diagnosis, systemic and supportive treatments offer a chance to extend the life span of patients with spinal metastases beyond several months to several years. With longer survival, the patients are at higher risk of metastatic tumour recurrence, especially patients without purely osteoblastic spinal metastases, a factor associated with poor local metastasis control. Thus, there is a need for a treatment that would ensure both durable pain control and metastatic tumour control in the patients with longer life expectancy, ensuring long-term palliation. With the introduction of high dose stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), radiation doses become “curative” as compared to “palliative” low doses of conventional radiation therapy. The treatment goal has shifted from short-term symptom control to long-term local metastasis control and makes SRS and SBRT a candidate treatment for painful spinal metastases. Despite its promising results, single-fraction SRS is associated with more recurrences in the epidural space and more frequent vertebral compression fracture (VCF). Hypofractionated SBRT may overcome limitations of single-fraction SRS by redefining the target volumes and improving metastatic disease control while minimising radiation-induced toxicity. We hypothesise that hypofractionated SBRT employing simultaneous integrated boost (SIB) allows radiation dose escalation in metastatic tumours with or without epidural involvement without

	increasing the risk of radiation-induced myelopathy and VCF. Radiotherapy dose escalation is expected to achieve long-term local metastasis control and thereby long-term pain control and long-term palliation. Hence, a randomised clinical trial with pain response at six months (primary end-point) and metastatic tumour control (secondary endpoint) in patients with painful spinal metastases and a longer life expectancy was initiated. We expect the results of this trial to be practice changing.
Study type/design	This is an international, multicentre, randomised, open-label, prospective, controlled study. This study additionally includes a prospective observational arm for patients not eligible for randomisation who are treated in analogy to arm A of the randomised arm.
Primary objective	**<u>Randomised arm</u>** To compare long-term pain response after dose-intensified image-guided hypofractionated SBRT employing SIB versus conventional radiation therapy for painful spinal metastases. **<u>Prospective observational arm</u>** To assess the long-term level of pain after dose-intensified image-guided hypofractionated SBRT employing SIB
Hypothesis	**<u>Randomised arm</u>** Dose escalation for painful spinal metastases using image-guided hypofractionated SBRT provides superior long-term pain response without adding toxicity as compared to conventional radiation therapy. **<u>Prospective observational arm</u>** To prospectively evaluate safety and efficacy of SBRT for vertebral metastases; no formal statistical endpoint will be tested.
End-points	**<u>Randomised arm</u>** ***Primary end-point:*** • Pain response - improvement by ≥ 2 points on the pain Visual Analogue Scale at 6 months post-treatment at the treatment site. ***Secondary end-points:*** • Local metastasis control; • Overall survival; • Cancer-specific survival; • Quality of life (QoL); • Acute and late toxicity. **<u>Prospective observational arm</u>** ***Primary end-point:*** • Pain response - improvement by ≥ 2 points on the pain Visual Analogue Scale at 6 months post-treatment at the treatment site. ***Secondary end-points:*** • Local metastasis control; • Overall survival; • Cancer-specific survival; • Quality of life (QoL);

	• Acute and late toxicity. **<u>Both arms</u>** ***Exploratory end-points:*** • Time interval from patient presentation to start of SBRT; • Central collection of all radiotherapy treatment plans for QA analyses. • Central collection of all follow-up imaging for normal tissue response analyses of the vertebra on CT and MRI imaging to dose-intensified SBRT.
Treatment	**<u>Both arms</u>** Stratification by centre. **<u>Randomised arm</u>** Patients eligible for the randomised arm will be randomised in a 1:1 ratio to either of the following regimes: ***Arm A (investigational) – investigational treatment*** Image-guided hypofractionated SBRT using SIB to escalate radiation dose in the tumour (high-dose target volume) while maintaining a conventional dose in the un-involved segments of the affected vertebrae (conventional-dose target volume). • in the case of no epidural involvement: 40 Gy and 20 Gy in 5 fractions to the high-dose and conventional-dose target volume, respectively; • In the case of epidural involvement: 48.5 Gy and 30 Gy in 10 fractions to the high-dose and conventional-dose target volume, respectively; or ***Arm B (control) – standard treatment*** External 3-dimensional conformal radiotherapy aiming at homogeneous irradiation of the affected vertebrae: each centre has to choose one fractionation protocol and use this one consistently within this study • 20 Gy in 5 fractions • 30 Gy in 10 fractions **<u>Prospective observational arm</u>** Patients eligible for the prospective observational arm (free of pain, purely osteoblastic metastases or refusal of randomisation), will be treated according to the investigational arm (arm A) of the randomised arm of the trial.
Number of patients	**<u>Randomised arm</u>** 160 participants will be recruited to the study. Based on prior research, a 40% pain response rate (≥ 2 point improvement based on VAS) is expected in the standard treatment group and a 30% difference in pain response is expected between groups. At least 80 patients are needed

	in each treatment group to have 90% power of detecting this difference at the 5% level of significance in the presence of a 30% dropout rate. **Prospective observational arm** The number of patients in the non-randomised part (observational arm) is not pre-defined because no formal statistical endpoint will be tested.
Inclusion criteria	**Both arms** Eligible patients have to provide written informed consent and must be able to understand and be willing to sign the written informed consent. Entry in the study is defined as the signing of the informed consent. • Established histological diagnosis of a malignant primary or metastatic tumour; • Histologically, radiologically or scintigraphically proven spinal metastasis; • Age ≥18 years old; • Karnofsky performance status ≥60%. • Life expectancy ≥ 1 year according to investigator`s estimate **Randomised arm** • Osteolytic or mixed osteolytic/osteoblastic lesion • Pain in the affected spinal region • Willingness to undergo randomisation • **Prospective observational arm** • Purely osteoblastic lesions or no pain in the affected spinal region or unwillingness to undergo randomisation
Exclusion criteria	**Both arms** • "Radiosensitive" histology of the primary tumour, e.g., lymphoma, small-cell lung cancer, multiple myeloma, germ cell tumours; • Progressive neurological symptoms/deficit; • More than 3 (cervical spine) or more than 4 (thoracic, lumber and sacral spine) continuously affected vertebrae in one target site; • More than 2 treatment sites; • Spinal Instability Neoplastic Score (SINS) 13 – 18 (unstable); • Unable to tolerate treatment (unable to lie flat and immobilized); • Previous radiotherapy of the region at the level of the affected vertebrae; • Previous radionuclide therapy within 30 days before stereotactic body radiation therapy; • Previous surgery (stabilisation) of the affected vertebrae; • Patients with allergy to contrast agents used in computer tomography (CT) and magnetic resonance (MR) imaging or patients who cannot be premedicated to use contrast agent; • Pregnant or lactating women; • Women of child bearing potential or sexually active males not willing to use effective contraception while on treatment and 3 months after the end of treatment;

	• Mental conditions rendering the patient unable to understand the nature, scope, and possible consequences of the study; • Patients unlikely to comply with protocol, i.e. uncooperative attitude, inability to return for follow-up visits, and unlikely to complete the study. **<u>Randomised arm</u>** • Purely osteoblastic lesions; • No pain in the affected spinal region • Unwillingness to undergo randomisation • **<u>Prospective observational arm</u>** • See "both arms" (no additional exclusion criteria)
Study procedures	**<u>Both arms</u>** ***Informed Consent*** Prior to any study specific measures (including screening measures), patients must sign the informed consent form, after nature, scope, and possible consequences of the clinical study have been explained to them in a form understandable for them. **<u>Both arms</u>** ***Screening*** All patients are screened for eligibility before treatment allocation. The following will be assessed: • Review of eligibility criteria; • Medical history; • Physical and neurological examination; • Height, weight, vital signs, Karnofsky performance status; • Recording of all preexisting symptoms; • Recording of pain and pain medications; • Recording of concomitant medications; • Radiology: o CT scans; o MR scans; o Bone scans or positron-emission tomography scans; • Pregnancy test for women of child bearing potential; • Decision of a study centre tumour board on radiation therapy for painful spinal metastases; • Health-related QoL as measured by the EORTC QLQ-C15-PAL, EORTC-BM22 and EQ-5D-5L patient reported questionnaires; • Willingness to undergo randomisation **<u>Randomised arms</u>** ***Treatment phase*** Patients will be treated according to arm A (investigational treatment) or arm B (standard treatment). ***In arm A***, patients immobilized in treatment position will undergo planning CT and MR. Two planning target volumes (PTVs) will be determined on CT and MR as follows: *1)* the high-dose gross tumour

	volume defined on CT/MR that is isotropically expanded with a 2 mm margin (the high-dose PTV) excluding the planning-at-risk volume (PRV) of the spinal cord and 2) the entire affected vertebra expanded isotropically with a 2 mm margin minus the high-dose PTV (the conventional-dose PTV or standard PTV, respectively). The spinal cord will be included into the conventional-dose PTV. In Arm A (investigational treatment) patients will receive image-guided static or rotational intensity-modulated radiation therapy with a prescription dose of 40 Gy and 20 Gy in 5 fractions to the high-dose PTV and conventional PTV, respectively, in the case of no epidural involvement; 48.5 Gy and 30 Gy in 10 fractions, if there is epidural involvement. There will be daily image-guided online correction of patient position errors. ***In Arm B***, patients will receive 3-dimensional conformal radiation therapy of the involved vertebrae using an institutional image-guidance protocol with a median prescription dose of 20 Gy in 5 fractions or 30 Gy in 10 fractions, depending on institutional protocol. For ***arm A*** and ***arm B***, the following procedures will be completed weekly during treatment: • Physical and neurological examination; • Weight, vital signs, Karnofsky performance status; • Assessment of pre-specified protocol-specific adverse events; • Recording of all other adverse events; • Recording of pain and pain medications; • Health-related QoL as measured by the EORTC QLQ-C15-PAL, EORTC-BM22 and EQ-5D-5L patient reported questionnaires (once at the last day of treatment). There will be a prospective collection of planning CT and MR scans, treatment plans and all follow-up images of all patients enrolled into the study. **<u>Prospective observational arm</u>** ***Treatment phase*** In the **Prospective observational arm**, patients will be treated exactly as patients in arm A of the randomised arm and they will undergo the same procedures. **<u>Both arms</u>** ***Post-treatment phase*** For all patients, the following will be completed within 1 month ±1 week (first follow-up visit): • Physical and neurological examination; • Weight, vital signs, Karnofsky performance status; • Assessment of pre-specified protocol-specific adverse events; • Recording of all other adverse events; • Recording of pain and pain medications; • Recording of concomitant medications;

	• Health-related QoL as measured by the EORTC QLQ-C15-PAL, EORTC-BM22 and EQ-5D-5L patient reported questionnaires. **<u>Both arms</u>** ***Follow-up visits*** Patients will be followed-up for 2 years after treatment completion or until death. Follow-up visits are scheduled at 3, 6, 12 and 24 months (±4 weeks) after treatment. The following procedures will be done at every follow-up visit: • Physical and neurological examination; • Weight, vital signs, Karnofsky performance status; • Assessment of pre-specified protocol-specific adverse events; • Recording of all other adverse events; • Recording of pain and pain medications; • Recording of concomitant medications; • Radiology as clinically indicated for osteolytic lesions, based on institutional protocol: CT and/or MR scans; • Health-related QoL as measured by the EORTC QLQ-C15-PAL, EORTC-BM22 and EQ-5D-5L patient reported questionnaires.
Study schedule	First quarter Q1 2016 (first patient enrolment) – Q4 2023 (last patient enrolment)
Sponsor-Investigator and Coordinating-Investigator	***Professor Doctor Matthias Guckenberger*** Department of Radiation Oncology University Hospital Zurich Raemistrasse 100 CH - 8091 Zurich Switzerland Phone: +41 44 255 29 30 Fax: +41 44 255 45 47 e-mail: matthias.guckenberger@usz.ch
Study centres	**Currently participating centres:** 20 sites in Switzerland and in Europe
Statistics	**<u>Randomised arm</u>** ***Sample size*** 160 participants will be recruited to the study. Based on prior research, a 40% pain response rate (≥ 2 point improvement based on VAS) is expected in the standard treatment group and a 30% difference in pain response is expected between groups. At least 80 patients are needed in each treatment group to have 90% power of detecting this difference at the 5% level of significance in the presence of a 30% dropout rate. ***Statistical analysis*** Statistical analysis will be done in three populations: *1)* Intent-to-Treat population (ITT) including all patients who were randomised and received at least one fraction of radiation therapy; *2)* Per Protocol population (PP) including all patients of the ITT who have received study treatment according to randomisation without significant protocol violations and *3)* safety-analysis set including all patients who were randomised and received at least one fraction of radiation therapy. To compare long-term pain control, Pearson's chi-square test with a continuity correction will be used on pain response rates across the two

	treatment arms. Wilson-method 95% confidence intervals will be provided for the pain response rate in each treatment group. The risk difference and its confidence interval will be provided as an effect measure, easily allowing for readers to calculate the 'number needed to treat'. Additionally, the odds ratio will be provided as a second effect measure. This measure allows for easy extension to logistic regression if other characteristics vary greatly across treatment groups. If daily oral morphine equivalent or epidural involvement vary greatly across treatment groups, a logistic regression model including treatment, daily oral morphine equivalent, epidural involvement, and centre will be used, which yields an odds ratio and its 95% confidence interval to summarize the difference in pain response between the treatment groups while controlling for other factors. The Kaplan Meier estimator will be used for overall survival across the two treatment groups. (Semi-) Competing risk methods will be used to address the following events: local metastasis recurrence, cancer-specific death, and death by other causes. Cumulative incidence functions and sub-distribution hazards accounting for competing risks will be computed. All safety analyses will be conducted on the safety-analysis set according to treatment received. For pre-specified protocol specific AEs, the point estimate of the difference between treatment arms, with 2-sided 95% CIs, will be provided. All other safety analyses will be presented in tabular format with the appropriate summary statistics for each treatment arm. QoL descriptive analysis will include the subset of the PP patients. **<u>Prospective observational arm</u>** ***Sample size*** The sample size will not be pre-defined since no formal statistical hypothesis will be tested. For the University Hospital Zurich, we assume ca. 40 patients. ***Statistical analysis*** The statistical analysis will be mainly descriptive and exploratory. We report mean and standard deviation for continuous variables and median and interquartile range for ordinal variables and number and percentage for categorical variables. For the primary outcome, the proportion of patients with clinically relevant pain reduction will be estimated with Wilson 95% confidence intervals. Kaplan Meier curves will be plotted for overall survival. Competing risk methods will be used for local metastasis control, cancer-specific survival, and overall survival. Descriptive statistics will be used to describe quality of life outcomes and safety outcomes. ***Interim Analysis*** If the trial fails to recruit at least 50% of the initially planned patients in the randomised arms until 12/2020 (originally planned recruitment end), an interim safety and efficacy analysis of both randomised and prospective observational arms will be conducted. If no safety concerns are raised after this interim analysis and there is a clinically relevant benefit of at least 10% for the experimental regimen

	regarding the primary endpoint, the recruitment will be continued. Otherwise, the study will be terminated due to slow accrual and futility.
GCP statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.