STUDY SYNOPSIS

Sponsor	Ghent University St. Pietersnieuwstraat 33 B-9000 Ghent
Study Title:	PEACE V: A randomized phase II trial for the Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM)
Short Title / Study ID:	STORM
Protocol Version and Date:	Version 3.1 (28.01.2021)
Trial registration:	Swiss National Clinical Trials Portal (SNCTP) (SNCTP000002947) ClinicalTrial.gov (NCT03569241)
Clinical Phase:	This is a randomized phase II trial
Background and Rationale:	A proportion of prostate cancer (PCa) patients develop a local, regional (N1) or distant (M1) relapse following curative local treatment. For both local and distant relapses, different treatment recommendations are made in the guidelines (EAU guidelines 2016). However, the entity regional nodal recurrence is not mentioned in the guidelines but is an emerging clinical situation since the introduction of choline and more recently PSMA PET-CT in the restaging of recurrent prostate cancer [1]. More specifically, a subgroup of these patients is being diagnosed with a recurrence confined to the regional lymph nodes and limited in number (oligorecurrence) using choline or PSMA PET-CT [2, 3]. As there are no specific treatment recommendations for these type of patients, different treatment approaches are currently used, mostly focusing on local ablative treatments using radiotherapy or surgery [4, 5]. These treatments are coined metastasis-directed therapy (MDT) [4]. MDT in combination with or without temporary ADT could delay the subsequent risk of progression, and even cure limited regional nodal recurrences [4]. Consequently, lifelong palliative ADT, with its toxicity and excess in non-cancer mortality [6] might be postponed. The proposed trial randomizes patients with oligorecurrent nodal prostate cancer following primary PCa treatment to either metastasis-directed therapy (MDT) (sLND or SBRT) or MDT plus WPRT (45 Gy in 25 fractions).
Objective(s):	**Primary Objective***:* o To compare metastases-free survival (MFS) between metastasis-directed therapy and metastasis-directed therapy with whole pelvis radiotherapy for oligorecurrent nodal prostate cancer. **Secondary Objectives:** o To compare clinical progression-free survival between arms o To compare biochemical progression between arms o To compare late toxicity between arms o To compare the quality of life between arms. o To compare the relapse pattern between arms o To compare time to start of palliative ADT, time to castration-resistant disease and overall survival between arms o Economical evaluation of different treatment arms o Sensitivity and specificity of imaging modality for patients receiving sLND as MDT o Biomarker discovery: To develop a miRNA panel predictive for treatment response using whole genome miRNA expression profiling.
Study design:	This is a randomised phase II trial

Inclusion / Exclusion criteria:	Inclusion criteria o Histologically proven initial diagnosis of adenocarcinoma of the prostate o Biochemical relapse of prostate cancer following radical local prostate treatment (radical prostatectomy, primary radiotherapy or radical prostatectomy +/- prostate bed adjuvant/ salvage radiotherapy) according to the EAU guidelines 2016. o Following radical prostatectomy, patients with a biochemical relapse are eligible in case a nodal relapse is detected in the pelvis even in the absence of prior postoperative prostate bed radiotherapy (adjuvant or salvage). o In case of a suspected local recurrence following primary radiotherapy, a biopsy should confirm local recurrence and patients with a confirmed local recurrence are eligible in case they also undergo a local salvage therapy. If imaging rules out local relapse, patients are eligible. o Nodal relapse in the pelvis on choline, PSMA or FACBC PET-CT with a maximum of 5 positive nodal lymph nodes. The upper limit of the pelvis is defined as the aortic bifurcation. o WHO performance state 0-1 o Age ≥18 years o Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial o Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations. Exclusion criteria: o Bone or visceral metastases o Para-aortic lymph node metastases (above the aortic bifurcation) o Local relapse in the prostate gland or prostate bed not suitable for a curative treatment o Previous irradiation of the pelvic and or para-aortic nodes o Serum testosterone level <50ng/dl or 1.7 nmol/L at time of randomization o Symptomatic metastases o Lymph node metastases in previously irradiated areas resulting in dose constraint violation as stipulated in part 5.2 o Contraindications to pelvic radiotherapy (chronic pelvic inflammatory bowel disease) o Contraindications to androgen deprivation therapy o PSA rise while on active treatment with (LHRH-agonist, LHRH-antagonist, anti-androgen, estrogen o Previous treatment with cytotoxic agent for PCa o Treatment during the past month with products known to influence PSA levels (e.g. fluconazole, finasteride, corticosteroids,…) o Other active malignancy, except non-melanoma skin cancer or other malignancies with a documented disease-free survival for a minimum of 3 years before randomization.

Number of Participants:	196 patients overall.
Statistical Considerations:	The sample size is based on the stratified Logrank test. A scenario analysis was then performed to reflect the different and reasonable possible values that the parameters can assume. The two-sided significance level alpha was set at 0.20 and the power maintained at 80%. In this chosen scenario, we estimated that the median progression-free survival following MDT is 24 months in arm A. Assuming uniform accrual over 48 months with 24 months additional follow-up time, we need a total of 196 patients to detect a 12-month difference in median PFS from 24 to 36 months taking into account a 15% rate of loss to follow-up.
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 well as all national legal and regulatory requirements.