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Zilli, Thomas ; Dirix, Piet ; Heikkilä, Reino ; Liefhooghe, Nick ; Siva, Shankar ; et al ; Guckenberger, Matthias

Abstract: Optimal local treatment for nodal oligorecurrent prostate cancer is unknown. The randomized phase 2 PEACE V-STORM trial will explore the best treatment approach in this setting. Early results on the acute toxicity profile are projected to be published in quarter 3, 2021.

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The multicenter, randomized, phase II PEACE V – STORM trial: defining the best salvage treatment for oligorecurrent nodal prostate cancer metastases

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Running Title: PEACE V-STORM: trial update

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With the widespread use of metabolic imaging, metachronous oligorecurrent nodal metastases are a clinical manifestation frequently observed in prostate cancer (PCa) patients relapsing after a primary curative treatment [1–5]. Although immediate or delayed androgen deprivation therapy (ADT) remains the standard treatment, metastasis-directed therapy (MDT) approaches including salvage lymph node dissection (sLND) and radiotherapy (RT) using focal stereotactic radiotherapy (SBRT) or whole-pelvis radiotherapy (WPRT) have been investigated to reduce disease progression or postpone the use of palliative ADT [6–11].

As the optimal local treatment for this patient group is unknown [1,2], we started the multicenter, randomized, phase 2 PEACE V-STORM trial (ClinicalTrials.gov NCT03569241) in June 2018. The aim is to explore the potential benefit in terms of metastasis-free survival (MFS) of an elective nodal approach with WPRT delivered as an alternative to focal SBRT or as adjuvant treatment after sLND in patients with oligorecurrent nodal PCa relapsing after primary treatment [12].

PCa patients with positron emission tomography (PET)-detected pelvic nodal oligorecurrence (5 nodes) following a primary radical local treatment (radical prostatectomy or prostate bed RT or definitive RT) were randomized 1:1 to MDT (sLND or SBRT) alone or to MDT (sLND or focal boost) with WPRT; both strategies were combined with 6 months of ADT (Fig. 1).

Patients were stratified according to the PET tracer used for restaging (choline, prostate-specific membrane antigen [PSMA], or fluciclovine) and the type of MDT (SBRT or sLND). Eligible patients have a prostate adenocarcinoma in biochemical relapse following radical local prostate treatment, with five or fewer positive lymph nodes in the pelvis (upper limit at the aortic bifurcation) as detected by PET imaging.

Exclusion criteria include the presence of extrapelvic metastatic disease (bone, visceral, or para-aortic lymph node metastases); a local relapse in the prostate gland or bed not suitable for curative treatment; previous irradiation of the pelvic and/or para-aortic nodes; previous treatment with a cytotoxic agent for prostate cancer; and other active malignancies.

The primary outcome is MFS, estimated as the time between randomization and the appearance of a metastatic recurrence (any M1) as suggested by PET imaging or death due to any cause.

Secondary outcomes include clinical progression free-survival (PFS; any new N1 or M1 recurrence); biochemical PFS; time to initiation of ADT; time to castration-resistant disease; PCa-specific survival; overall survival; acute and late toxicities (Common Terminology Criteria for Adverse Events v4.0); and quality of life (European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-PR25 questionnaires). The study also includes a translational section aimed at developing a miRNA panel predictive for treatment response.

With accrual of 48 and 24 months of follow-up, a total of 178 patients are needed to detect a 12-month difference in median MFS from 24 (arm A) to 36 months (arm B), considering a 5% rate of loss to follow-up (two-sided significance level set at $\alpha = 0.020$ and power maintained at 80%). Survival endpoints will be estimated using the Kaplan-Meier survival analysis method, and treatments will be compared using a stratified log-rank test. The effects of treatment and baseline characteristics will be assessed using Cox proportional hazards models.

From June 8, 2018 to October 11, 2020, 146 (82%) of a planned 178 participants have been included, of whom 145 (81%) were randomized at 18 of 24 participating centers in Europe and Australia (Fig. 2). Seventy-three patients have been included in arm A and 72 in arm B, and six patients have dropped

out. PSMA PET was the imaging modality most used for restaging (n = 123, 85%), with choline PET used for the remaining 22 patients (15%). sLND was pro-posed as the MDT strategy for nine patients, of whom five were randomized to arm A and four to arm B. Among the 136 patients treated with RT, focal SBRT (arm A) was used in 68 patients, with a similar proportion of patients treated with WPRT (arm B).

Although 75% of panelists in the 2019 Advanced Prostate Cancer Consensus Conference recommended ADT and local treatment of all lesions for the majority of patients with oligorecurrent PCa [13], scientific evidence on MDT strategies is mostly based on retrospective series, with the best treatment approach for these patients remaining a matter of debate [2,14]. Available retrospective studies comparing WPRT and SBRT techniques seem to favor comprehensive pelvic irradiation over focal RT in terms of improved freedom from failure and fewer nodal recurrences, at the cost of a potential increase in toxicity [1,15,16]. Using well-defined endpoints and treatment approaches, the PEACE V-STORM trial is the first phase 2 randomized controlled trial that will explore the possibility of improving MFS by adding WPRT to either sLND or SBRT in combination with short-term ADT for PCa patients with nodal oligorecurrent disease. Early results on the acute toxicity profile are projected to be published in quarter 3 2021.

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Figure legend

Figure 1. PEACE V-STORM inclusion rate and recruiting centers.

Declarations

Ethics approval and consent to participate

Signature of the informed consent will be obtained from all patients before inclusion in the study. This study was approved by the Ethics committee of the Ghent University Hospital (EC/2018/0130) and for all participating centers. The study is registered on Clinicaltrials.gov (NCT03569241) and Swiss National Clinical Trials Portal (SNCTP000002947).

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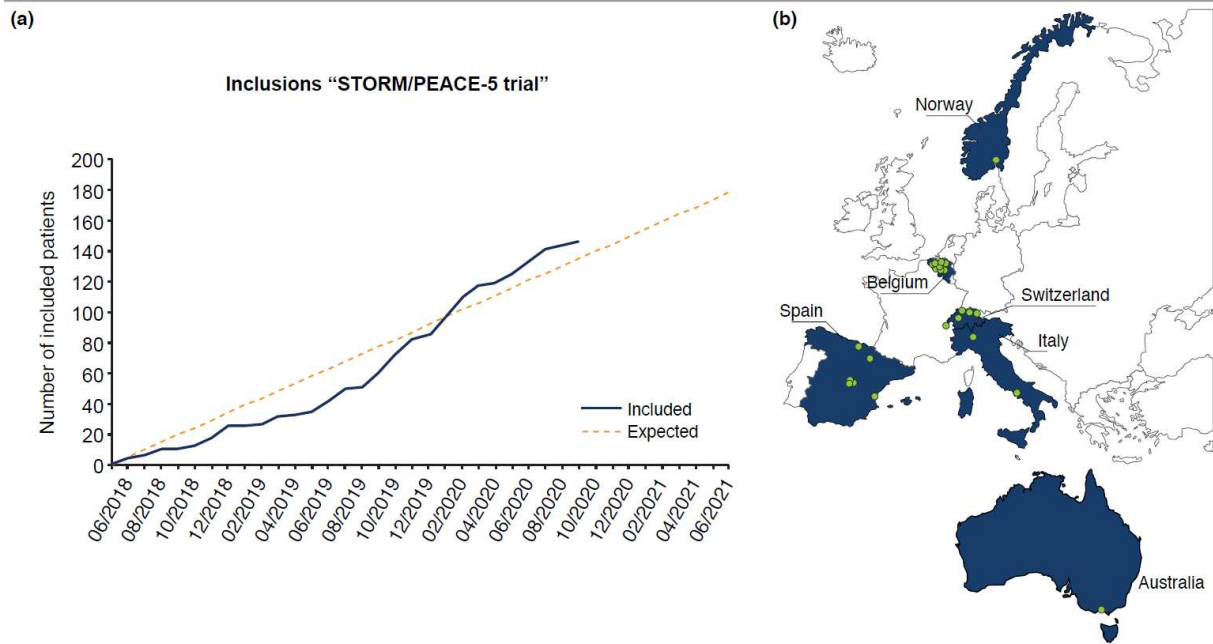


Fig 1