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Randomised phase II trial of stereotactic body radiotherapy in combination with checkpoint inhibitors in metastatic castration-resistant prostate cancer (CheckPRO): a study protocol

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ABSTRACT

Introduction Immunotherapy with checkpoint inhibitors (CPIs) has revolutionised cancer treatment but has no convincing effect in metastatic castration-resistant prostate cancer (mCRPC). It has been suggested that a combination of CPI and hypofractionated stereotactic body radiotherapy (SBRT) may work synergistically, and recent trials have supported this. We hypothesise that adding SBRT to CPI treatment can improve response rates in patients with mCRPC.

Methods and analysis The CheckPRO trial is an open-label, randomised, two-stage, phase II trial. We aim to enrol and randomise 80 evaluable patients with mCRPC who progressed following ≥2 lines of treatment. Enrolment started in November 2019 with 38 months expected enrolment period. The participants receive treatment for 52 weeks including four cycles of ipilimumab and nivolumab with or without concomitant SBRT (24 Gray in three fractions) to a single soft tissue or bone metastasis, followed by 10 cycles of nivolumab. Participants are followed until progression, death, or for 12 months after the end of treatment.

Co-primary endpoints are the objective response rate and prostate-specific antigen (PSA) response rate. Secondary endpoints include safety, radiographic progression-free survival, clinical benefit rate, duration of response, PSA-progression-free survival beyond 12 weeks, quality of life and overall survival. Exploratory endpoints include translational analyses of tumour biopsies and consecutive blood samples. Biopsies from metastatic sites are collected at baseline, before the third treatment and at the end of treatment. Blood sampling for immune monitoring and circulating tumour DNA is performed consecutively at baseline and every radiographic assessment.

Ethics and dissemination This study follows the Helsinki Declaration and is approved by the Danish Ethics Committee System (journal no. H-19016100). All participants must receive written and oral information and provide a signed informed consent document prior to inclusion. The study results will be published in an international peer-review journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial investigates the effect of checkpoint inhibitors with or without stereotactic body radiotherapy for metastatic castration-resistant prostate cancer.
⇒ Baseline and on treatment tumour tissue biopsies and immune cell monitoring.
⇒ Single participating site allowing consistency of procedures and evaluations.
⇒ No comparison with standard treatment and not blinded.

Trial registration number EudraCT number: 2018-003461-34. clinicaltrials.gov ID NCT05655715.

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is considered non-immunogenic, with limited survival benefit by monotherapy with checkpoint inhibitors (CPIs) in unselected patients.[1–3] Dual therapy with CPIs has been tested in two phase II trials with clinically meaningful response rates in selected patients with mCRPC.[4 5]

Prostate cancer is mirrored by a 'cold' tumour microenvironment (TME) with many immunosuppressive cells and few $CD8^+$ tumour-infiltrating lymphocytes.[6] This immune-suppressive TME with a low tumour mutational burden (TMB) is suggested to be a critical factor of unresponsiveness to CPI treatment.[7 8] It is noteworthy that in nearly one-third of patients with mCRPC, the tumour cells had a programmed cell death ligand 1 (PD-L1) expression of >1%, assessed by using immunohistochemistry, which suggests a rationale for CPI.[9]

New treatment strategies employing multimodality combinations and improved patient selection are needed to increase the clinical benefit for patients with non-immunogenic cancers. For mCRPC, combinations of CPI and radiotherapy, poly (ADP-ribose) polymerase inhibitors or new-generation anti-androgen targeted therapy have been investigated in multiple trials, however none of these are used as standard therapy in Denmark yet.[8 10]

Preclinical and early clinical studies have indicated that hypofractionated high-dose radiotherapy, such as stereotactic body radiotherapy (SBRT), may enhance the response rate of CPI treatment outside the irradiated lesion,[11–13] which is known as the abscopal effect.[14] It is suggested that the abscopal effect is initiated by a combination of tumour antigen release and modulation of the immunogenicity of the TME, which leads to immunogenic activation and death of the cancer cells.[15] The pretreatment TME immunogenic status is important for the response to CPI and needs further investigation.[16] A phase III trial found a 5-year overall survival benefit of 5.2% of using ipilimumab combined with palliative bone radiotherapy compared with palliative radiotherapy alone in mCRPC.[17] The optimal timing, dose, and fractionation of radiotherapy as an adjuvant to CPI treatment is not known.[18]

In the CheckPRO trial, we investigate the potential synergistic effect of combining SBRT of a single soft tissue or bone metastasis with ipilimumab and nivolumab in patients with mCRPC and perform translational analyses on tissue and blood in search for predictive biomarkers for efficacy and toxicity.

METHODS

Objectives

The primary objective is to evaluate the response rate of ipilimumab and nivolumab with or without SBRT in patients with mCRPC. The secondary objectives are to study safety, quality of life (QoL) and efficacy, defined as the clinical benefit rate (CBR), radiographic progression-free survival (rPFS) and overall survival (OS). Exploratory objectives are to identify immunological and genetic, predictive and prognostic biomarkers.

Study design

The CheckPRO trial is an investigator-initiated, single-centre randomised phase II trial at the Department of Oncology, Copenhagen University Hospital, Herlev and Gentofte Hospital, Denmark. The first patient first visit was 30 November 2019 and expected last patient last visit is the 31 December 2024. Participants are randomised 1:1 to ipilimumab and nivolumab with or without SBRT to a single metastatic lesion stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). Figure 1 shows the trial design. This trial is registered at the European Union Clinical Trial Register (https://www.clinicaltrialsregister.eu/), EudraCT number: 2018-003461-34 and at https://clinicaltrials.gov, identifier: NCT05655715.

Inclusion criteria

Eligible participants are men aged ≥18 years with mCRPC with a primary histological or cytological confirmed prostatic adenocarcinoma or poorly differentiated carcinoma (neuroendocrine differentiation is allowed), surgical or medically castrated with serum testosterone levels <50 ng/dL (1.73 nM), an ECOG performance status 0–1 (PS), and with a life expectance above 3 months. Participants must have progressive disease (PD) after a second line of treatment in a castration-resistant setting, defined as rising prostate-specific antigen (PSA) levels in at least two consecutive measurements (separated by a minimum of 1 week and ≥2 ng/mL), PD according to RECIST version .1.1 on CT or MRI scans, or new bone lesions on bone scintigraphy or fluorine positron emission tomography per Prostate Cancer Clinical Trials Working Group V.3 (PCWG3).[19] The two lines of treatment must include one line of androgen receptor (AR) axis targeted therapy (abiraterone acetate, enzalutamide or investigational AR targeted drug) and one line of taxane-based chemotherapy.

Participants must have adequate organ function defined as absolute neutrophil count ≥1.5 × 10^9/L, platelets >100 × 10^9/L and haemoglobin ≥90 g/L (5.6 mmol/L, independent of transfusion ≤14 days), bilirubin <1.5× upper limit of normal (ULN), international normalised ratio of prothrombin time ≤1.5, aspartate aminotransferase

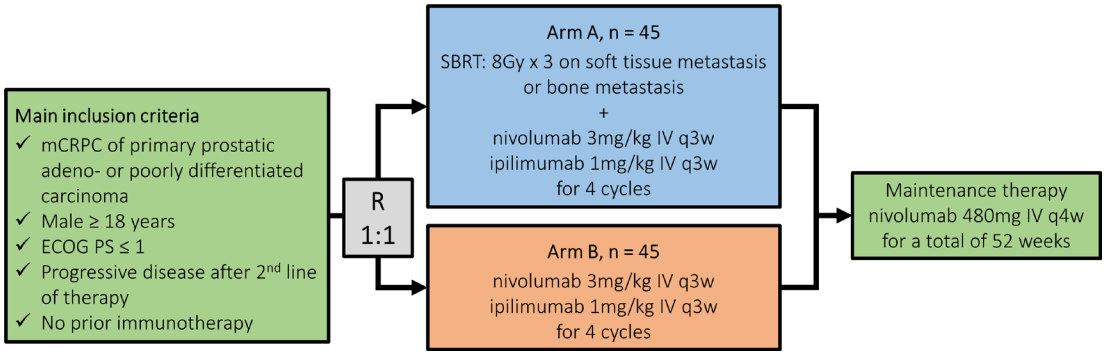

Figure 1 The CheckPRO study design. ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; q3w, every 3 weeks; q4w, every 4 weeks; R, randomisation; SBRT, stereotactic body radiotherapy.

(AST) and alanine aminotransferase (ALT) <3× ULN without liver metastases, and AST and ALT <5× ULN for participants with liver metastases and serum creatinine <1.5× ULN.

Participants must be willing to have an image-guided percutaneous biopsy of a soft tissue metastatic lesion if considered safe. Any participant with female partners of childbearing potential are advised to use a safe contraception. All participants must sign an independent ethics committee-approved informed consent.

Exclusion criteria

Participants are not included in the CheckPRO trial if they have previously received immunotherapy with CPIs or other antibodies or drugs targeting T-cell costimulation or immune pathways. Participants with a history of other cancers in remission (excluding curatively treated non-melanoma skin cancer, carcinoma in situ, or superficial bladder cancer) are permitted to be enrolled if the last dose of chemotherapy was completed > 6 months prior to the first dose of ipilimumab and nivolumab. The participants must not receive any antineoplastic therapy at least 28 days before the first dose of the study drugs. Treatment with denosumab or bisphosphonate is allowed. Participants with persistent adverse events from prior cancer treatment (except alopecia) that has not resolved to a maximum of grade 1 according to common terminology criteria for adverse events (CTCAEs) will be excluded, however, the sponsor may permit ongoing grade 2 non-haematologic toxicity related to the most recent treatment. Participants with untreated or symptomatic central nervous system or spinal cord compression metastases are excluded.

Participants with a medical history of allergy to study drug components, severe hypersensitivity reaction to any monoclonal antibody, known human deficiency viral infection, AIDS, chronic hepatitis B or C infection, active or suspected autoimmune disease are not permitted except vitiligo, type 1 diabetes, residual hypothyroidism or psoriasis (without systemic treatment). Participants with a condition requiring systemic treatment with either corticosteroid (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration are excluded but inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

The presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and in the opinion of the principal investigator, would make the participant inappropriate for entry into the study.

Eligible participants and enrolment

Participants can be referred from any outpatient oncological or urological clinics in Denmark. On consent, candidates for the trial are screened for eligibility and scheduled for a multidisciplinary SBRT team conference before randomisation. Concealed randomisation is performed, and data are kept in the REDCap electronic data capture tools database, hosted at the Capital Region of Denmark.[20]

Interventions

Study treatment includes nivolumab (Opdivo, Bristol-Myers Squibb) 3 mg/kg over 30 min intravenous followed by ipilimumab (Yervoy, Bristol-Myers Squibb) 1 mg/kg over 90 min as an intravenous infusion, 30 minutes after completion of the nivolumab infusion in both treatment arms. Ipilimumab and nivolumab will be given in combination every third week (q3w) for four cycles, followed by a fixed dose of nivolumab 480 mg intravenous every fourth week (q4w). The nivolumab fixed-dose will continue for up to 52 weeks from treatment start unless in the event of PD, unacceptable toxicity, withdrawal of consent, or clinical deterioration according to the investigator's judgement. No dose escalation or reduction is permitted.

All eligible participants are discussed at a multidisciplinary SBRT team conference, and one metastasis is selected for possible SBRT. Accessibility for biopsy, risk of radiation toxicity, distance to a possible soft tissue reference metastasis (for biopsy in arm A) and size <5 cm are all criteria that are considered when choosing the metastasis for SBRT. Soft tissue SBRT targets are preferred to bone metastases for translational purposes (ie, acquiring pre-treatment biopsies from the irradiated metastasis).

Participants randomised to arm A receive SBRT to a single soft tissue or bone metastasis. The prescribed dose is 24 Gray (Gy) in three fractions started on the same day as the first dose of ipilimumab and nivolumab, see figure 2. Participants are treated in a supine position with support from a moulded vacuum bag and knee support. A planning CT scan is acquired with a maximum 3 mm slice thickness. Intravenous contrast enhancement is used per standard procedures. Lung targets are planned with breathing correlated CT scan.

The metastasis selected for SBRT is outlined as a gross tumour volume (GTV). Delineation is guided by MRI for liver and bone metastases, or if needed. Planning target volume (PTV) includes the GTV with an isotropic safety margin of 5 mm for soft tissue metastases and 2 mm for bone metastases.

An inhomogeneous dose plan is made using intensity-modulated radiotherapy or volumetric modulated arc therapy technique aiming at a 95% isodose coverage of the GTV and a 67% isodose coverage of the PTV. Dose constraints include a maximum dose (D0.1cc) <140% within the GTV and ≤107% outside the GTV. Dose constraints to organs at risk are prioritised higher than GTV and PTV coverage. Depending on the anatomical location of the organs at risk, the constraints are kept strictly in line with previously published recommendations.[21 22] Daily volumetric image guidance is used to deliver the SBRT with an external photon beam (6–15 MV) on a CT or MR linear accelerator.

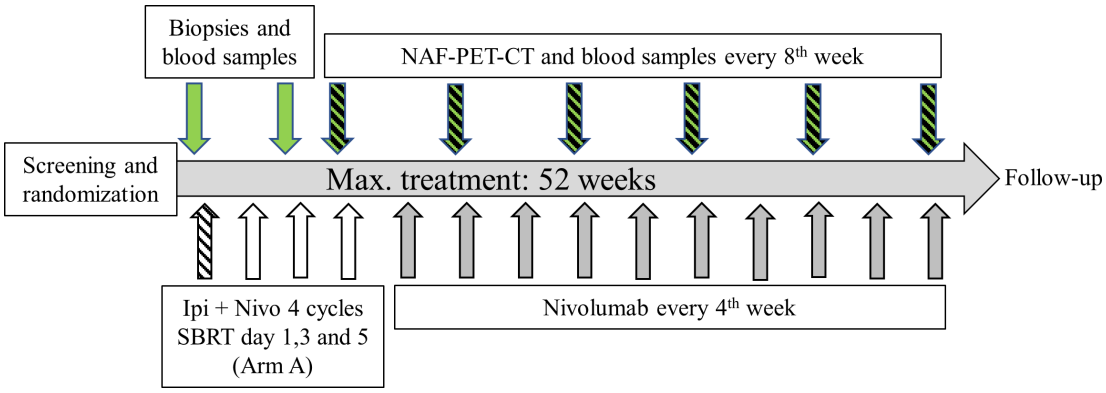

Figure 2 Flow chart of study treatment and biomarker sampling. The arrows specify time points of study treatment, biomarker sampling and radiographic assessments. Solid green arrows specify biopsies and blood samples for ctDNA and immune monitoring; green and black striped arrows specify radiographic assessment and blood samples for ctDNA, immune and protein biomarkers; white and blank striped arrow specifies SBRT during day 1 in the first cycle of ipilimumab and nivolumab; grey arrows indicate the maintenance nivolumab treatment. ctDNA, circulating tumour DNA; Ipi, ipilimumab; Nivo, nivolumab; SBRT, stereotactic body radiotherapy.

Primary, secondary, and exploratory endpoints

The coprimary endpoints are the objective response rate (ORR) and PSA response rate. The ORR is defined as the fraction of participants with a partial response (PR) or complete response (CR) per RECIST V.1.1 for participants with measurable disease. The ORR assessment will not include the irradiated lesion. The PSA response rate is defined as the fraction of participants with ≥50% decline from baseline at any time from treatment initiation (confirmed after at least 3 weeks).

Secondary endpoints are safety per CTCAE V.5.0, rPFS defined as per PCWG3 with the '2+2 rule' for bone metastases (online supplemental table S1), RECIST V.1.1 for soft tissue metastases and clinical progression (all participants), rPFS per iRECIST, CBR defined the fraction of participants with partial response, complete respone, or stable disease (at 6 months) by RECIST V.1.1, ORR by iRECIST, duration of response, PSA-progression-free survival beyond 12 weeks per PCWG3, rPFS and overall survival (OS) rate at 6 months and 1 year, median OS, and quality of life using EORTC QLQ-C30.

Exploratory endpoints include translational analyses of tumour biopsies and consecutive blood samples to assess genetic and immunological biomarkers of response, toxicity and survival.

Safety

Subjects will be evaluated for safety if they have received any study drug. Assessments of adverse events will be performed at each visit during the treatment phase. Adverse events and laboratory values will be graded according to the National Cancer Institute CTCAE V.5.0. Physical examinations are performed at baseline and as clinically indicated. Laboratory adverse events (eg, suspected drug-induced liver enzyme elevations) will be monitored during the follow-up phase via onsite/local laboratories until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible. Additional measures, including non-study-required laboratory tests, will be performed as clinically indicated.

A Trial Safety Committee will review relevant data for the safety of the participants in this trial. The sponsor will provide an annual safety report throughout the study period.

Baseline and follow-up evaluation

Baseline medical and surgical history and medication information will be obtained, followed by a physical examination, baseline laboratory test, and an electrocardiogram at the first visit. All participants must be restaged by ^{18}Flour-sodium fluoride positron emission tomography combined with contrast-enhanced computed tomography (NaF-PET-CT) scan within 28 days prior to first treatment. Participants will be followed every eighth week with NaF-PET-CT scans during active treatment and up to 1 year after the end of treatment. The scans will be prospectively evaluated by a specialist in onco-radiology and a specialist in nuclear medicine. The investigator is responsible for the clinical treatment decisions based on the response evaluation.

At the end of treatment, the participant will receive a safety follow-up visit 30 days after the last dose of the study drugs. All participants will have a follow-up for OS at 6 months and 1 year. In the case of PD before 52 weeks of treatment, the participants will be referred to subsequent standard treatment. If PD occurs after the completion of the 52 weeks treatment, a re-introduction of the study treatment can be given until PD. The re-introduction treatment consists of ipilimumab and nivolumab four times followed by nivolumab without SBRT until PD or for maximum 52 weeks. Participants receiving re-introduction of the study treatment will be evaluated with a NAF-PET-CT every 8 weeks and new biopsies will be performed before, at third cycle of ipilimumab and nivolumab, and at end of reintroduction treatment.

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD with new lesions on a subsequent scan (pseudoprogression).[23] Participants can continue treatment beyond the initial RECIST V.1.1 defined PD (measurable disease) or by the PCWG3 '2+2' rule of PD for new metastatic bone lesions (non-measurable disease, online supplemental table S1), if there is an investigator-assessed clinical benefit.[19] Investigator-assessed clinical benefit is conditional on that the participant tolerates the study drugs, has a stable performance status and that treatment beyond progression will not delay further needed treatment. Any PD according to RECIST V.1.1 leading to treatment beyond progression (ie, unconfirmed PD) should be confirmed with an additional radiographic assessment within 6 weeks of the first assessed PD.

Sample size and the two-stage procedure

The sample size calculations are based on a two-stage design for randomised phase II trials with two experimental treatment arms and PSA decline ≥50% as the endpoint.[24] At the time of sample size calculation, only response rates of single-agent CPI for mCRPC were available and reported up to 10% (null hypothesis). Overall, within each arm, a sample size of 40 is required to confirm the alternative hypothesis that the PSA 50% decline response rate is ≥25%. We expect a 10% dropout rate before the first evaluation, and 45 participants will be included in each arm. Additionally, we have prespecified the type 1 error to ≤5% of mistakenly selecting the inferior treatment for further study when the response rate in the inferior arm is lower than that in the unselected arm by 10%; and the power to ≥80% of selecting the superior treatment correctly for further study when the response rate in the superior arm is greater than or equal to 25% (alternative hypothesis) and also larger than that in the unselected arm by 20%. The first stage includes 20 participants in each arm. If less than two participants in one or both treatment arms have PSA decline 50%, the treatment arm or study is terminated. If only one treatment arm continues (≥2 responses in any arm with ≥5 in difference between arm A and B), 20 additional participants will be enrolled in the promising treatment arm. If both treatment arms have ≥2 responses but <5 in difference in the first stage, both treatment arms continue to the second stage. Any treatment arm with observed responses for ≥8 out of 40 participants after complete enrolment may be considered promising for further investigation. However, in case of ≥8 responses with PSA decline ≥50% are observed in both arms, a difference of ≥5 responses in between arms allows to select the superior treatment arm.

Soft tissue metastases in mCRPC are a bad prognostic factor, especially liver metastases.[25] During the second amendment, where patients with predominant bone metastases could be enrolled, we chose not to stratify according to soft tissue metastasis versus only bony metastases. When the amendment was implemented, 31 participants had been enrolled, given a minimum of 40% of participants with soft tissue metastases in the whole study population. We expected that up to 80%–90% of new participants would have only bone metastases; hence a stratification would have only a minor statistical impact given the anticipated sample size. Furthermore, by including participants with only bone metastases, the participants would be in earlier phases of their disease, given a 'lead-time bias,' which will be accorded for in interpreting the study results. We will present the data as a comprehensive table that can help distinguish between the different participant groups.

Tissue sampling and translational analyses

The participants will have an ultrasound-guided or CT-guided percutaneous 16-gauge core-needle biopsy taken from one soft tissue metastasis in arm B and two soft tissue metastases in arm A if considered safe by the investigator. The best available metastases outside the prostatic bed with the least risks for the patient would be selected, including loco-regional metastases. The two biopsies in arm A will include the SBRT target and a non-SBRT metastasis at least 2 cm distance from the target. Participants enrolled in the study will have a biopsy taken at three time points: at baseline, before the third cycle of ipilimumab and nivolumab (ie, at 6 weeks) and if possible, at progression (figure 2). Each tumour biopsy will be divided into two parts: one part will be evaluated by immunohistochemistry and the other with genetic analyses. The hypothesis is that response and treatment-related toxicity can be predicted based on the genomic and immunogenic profile of the tumour cells, TME, and blood.

Consecutive blood sampling for monitoring of peripheral mononuclear cells (PBMCs), circulating tumour DNA and protein biomarkers will be collected at each biopsy time point and each NaF-PET-CT scan every eighth week. Methodologies for circulating tumour nucleic acid identification may include but are not limited to DNA profiling or targeted gene sequencing, as new data and methodologies emerge. Immune monitoring of PBMCs will be performed by flow cytometry, and we will use a comprehensive panel focusing on T-cells and myeloid cells.

The tumour tissue biopsies will be investigated with a genomic sequencing of tumour driver and suppressor genes, TMB and RNA and microRNA profiling. The TME will be investigated by immunohistochemistry to characterise the immune-composition of tumour-infiltrating cells and PD-L1 expression of the tumour cells.

Statistical analyses

The database will be locked for analyses with data cut-off 1 year after the last patienthad last treatment. The co-primary endpoints will be analysed in an intention-to-treat analysis and a per-protocol analysis, including participants who received at least one cycle of nivolumab and ipilimumab and have minimum one follow-up measurement

(eg, radiographic assessment or PSA). The toxicity analyses will be based on the participants who received at least one cycle of ipilimumab and nivolumab with or without SBRT. The binominal test will be used to assess the response rates with 95% CIs. Categorical variables will be analysed with Fisher's exact test and the Kruskal-Wallis test for >2 groups. Radiographic PFS is defined as the time from treatment start until progression per PCWG3 (online supplemental table S1), the death of any cause, clinical progression or censored at last radiographic assessment. Overall survival is defined as the time from randomisation until death by any cause or last follow-up. Survival statistics will be calculated by the Kaplan-Meier method.[26] Flow cytometry data will be analysed based on the median fluorescence intensity and percent parent. All statistic calculations will be performed using SPSS (SPSS, Illinois, USA) and R statistics (RCRAN project, V.4.03). The level of significance is set at $p<0.05$.

Monitoring

This study is conducted in accordance with Good Clinical Practice and monitored by the Good Clinical Practice Unit (Copenhagen University Hospital, Frederiksberg Hospital, Denmark) as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC.

Ethics and dissemination

This study follows the Helsinki Declaration and is approved by the Danish Ethics Committee System (journal no. H-19016100). All participants must receive written and oral information and provide a signed informed consent document prior to inclusion. Participants are not offered compensation. The study results, positive, negative or inconclusive will be published in an international peer-review journal.

Patient and public involvement

When planning this trial, patients and the public were unfortunately not involved in designing, conducting or reporting the CheckPRO trial. However, we will consult the relevant patient cancer societies regarding disseminating the study results to the public.

Accrual and amendments

The CheckPRO trial has an expected enrolment period of 38 months. At the time of submission of this manuscript, 40 participants were randomised, and biopsies were obtained from 31, 24 and 8 participants at baseline, prior to third cycle and end of treatment, respectively. Biopsies were not obtained from four patients who had only bone metastases. During the COVID-19 pandemic, trial recruitment was paused from March 2020 until May 2020, figure 3. The protocol has been amended twice. The first amendment was in January 2020 by upgrading the radiographic assessments from a CT plus NaF-PET to a combined NaF-PET-CT scan at all timepoints. In December 2021, a second amendment was approved

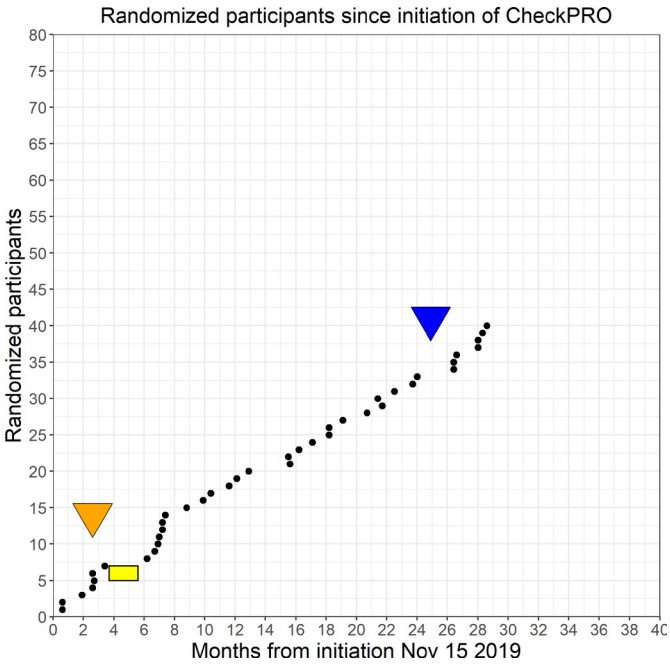

Figure 3 Enrolment rate and amendments. The yellow rectangle illustrates the first national lockdown during the first wave of the COVID-19 pandemic in Denmark. Orange triangle, first amendment (radiographic assessment). Blue triangle, second amendment approval (change of endpoint and inclusion criteria).

(V.3.1) due to a low enrolment rate. In the primary study protocol, a inclusion criteria stated that only participants with at least two measurable soft tissue metastases defined by RECIST V.1.1 were eligible for CheckPRO. This criterion was applied since at least two measurable soft tissue metastases were needed to have at least one measurable target lesion per RECIST V.1.1 (ie, the irradiated metastasis in patients in arm A was a non-target lesion). This happened to be a too small study population. We deleted this inclusion criterion, allowing enrolment of participants with mCRPC and measurable or non-measurable metastases. The primary endpoint was accordingly changed to a coprimary endpoint to include participants with non-measurable disease (ie, only bone metastases or non-measurable soft tissue metastases). See online supplemental file 2 for the full study protocol and online supplemental file 3 for the translated Patient Information and Consent Form.

DISCUSSION

To our knowledge, this is the first trial investigating whether ipilimumab and nivolumab with or without SBRT are feasible and effective for patients with mCRPC. The trial is a randomised, single-centre, phase II trial. We use a subablative SBRT dose of 24 Gy in three fractions equal to a biological equivalent dose of 43.2 Gy ($\alpha/\beta=10$) to stimulate the immune response as first proposed in a preclinical setting.[12] The use of repeated high-dose SBRT has recently been supported by Lin *et al* 2021, who

reported that a high single dose of SBRT induced a relevant immunogenic response, followed by a high immune-suppressing response.[27] A recently published phase II trial by Kwan *et al* 2021, reported a favourable ORR of 33% in patients with mCRPC treated with avelumab and SBRT of 20 Gy at two time points in the ICE-PAC trial.[28] These findings support the rationale for repeated SBRT in the immune-radiotherapy setting.

In the present study, the setup with consecutive tumour biopsies and blood samples for immunological monitoring will provide a unique opportunity to explore potential biomarkers of response and toxicity.

Ongoing clinical trials are currently investigating the effect of ipilimumab and nivolumab for highly selected patients with mCRPC and a positive immune signature, aiming to achieve an increased clinical benefit (eg, NCT02601014 and NCT04717154).[29 30] Preliminary results from the NEPTUNES trial (NCT03061539) reported a favourable response rate in highly selected and pretreated patients, with a composite response rate of 26%.

We acknowledge the limitations of the present study, including a small anticipated sample size, in comparison to the large and heterogeneous patient population with mCRPC worldwide. The CheckPRO trial is designed to investigate both response and new biomarkers. Response evaluation in mCRPC with bone metastases remains challenging, and in the light of the prostate-specific membrane antigen PET (PSMA-PET) era, the use of NaF-PET-CT might also be a limitation in the future. Furthermore, we amended the protocol after 20 months of enrolment due to an unexpected low enrolment rate. The main change in the amendment was the omission of the inclusions criteria requiring at least two measurable soft tissue metastases. This allowed patients with bone-only metastatic disease to be included, hence a more representable study population but at the cost of fewer soft tissue biopsies for the translational analyses.

The response evaluation in patients with mCRPC bone-only metastatic disease remains a challenge. We chose a coprimary endpoint with ORR and PSA response of ≥50% decline according to PCWG3 and in line with other studies of mCRPC and CPI treatment to evaluate patients with non-measurable disease.[3 28]

In conclusion, the CheckPRO trial evaluates the response rate and safety of adding SBRT to double CPI treatment in heavily pretreated patients with mCRPC. Additionally, translational analyses will be performed to find possible predictive immune and genetic biomarkers supporting precision medicine for patients with mCRPC.

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Contributors RLE, DLN, HL, NJS, ST and GFP planned and conducted the study. NJS and RLE drafted this manuscript and NJS submitted the manuscript after approval from the coauthors. IMS, HH, TL, EH and GA-F planned and conducted the translational and radiographic assessments and provided relevant equipment.

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Competing interests DLN, EVH, GA-F and ST have no conflict of interest. NJS has received conference participation from Pfizer Inc and a research grant from Herlev Hospital and Rigshospitalet, sponsored by Varian Medical Systems. Within the last two years IMS has received honoraria for consultancies and lectures from IO Biotech, Novartis, MSD, Pierre Fabre, BMS, Novo Nordisk, TILT Bio; research grants from IO Biotech, BMS, Lytix, Adaptimmune, TILT Bio. Within the last two years GFP has received conference participance from MSD, Daiichi Sankyo and Pfizer Pierre Fabre. Research grants from Varian Medical Systems and honoraria for consultancies and lectures from Astra Zeneca. RLE has received honoraria for consultancies and lectures from Amgen and received funding of study drugs from Bristol-Myers Squibb in the CheckPRO trial.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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