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Original Research

Nivolumab plus docetaxel in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer: results from the phase II CheckMate 9KD trial

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KEYWORDS
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Abstract ***Background:*** Docetaxel has immunostimulatory effects that may promote an immunoresponsive prostate tumour microenvironment, providing a rationale for combination with nivolumab (programmed death-1 inhibitor) for metastatic castration-resistant prostate cancer (mCRPC).
Methods: In the non-randomised, multicohort, global phase II CheckMate 9KD trial, 84 patients with chemotherapy-naive mCRPC, ongoing androgen deprivation therapy and ≤2 prior novel hormonal therapies (NHTs) received nivolumab 360 mg and docetaxel 75 mg/m^2 every 3 weeks with prednisone 5 mg twice daily (≤10 cycles) and then nivolumab 480 mg every 4 weeks (≤2 years). The co-primary end-points were objective response rate (ORR) and prostate-specific antigen response rate (PSA_{50}-RR; ≥50% decrease from baseline).
Results: The confirmed ORR (95% confidence interval [CI]) was 40.0% (25.7–55.7), and the confirmed PSA_{50}-RR (95% CI) was 46.9% (35.7–58.3). The median (95% CI) radiographic progression-free survival (rPFS) and overall survival (OS) were 9.0 (8.0–11.6) and 18.2 (14.6–20.7) months, respectively. In subpopulations with versus without prior NHT, the ORR was 38.7% versus 42.9%, the PSA_{50}-RR was 39.6% versus 60.7%, the median rPFS was 8.5 versus 12.0 months and the median OS was 16.2 months versus not reached. Homologous recombination deficiency status or tumour mutational burden did not appear to impact efficacy. The most common any-grade and grade 3–4 treatment-related adverse events were fatigue (39.3%) and neutropenia (16.7%), respectively. Three treatment-related deaths occurred (1 pneumonitis related to nivolumab; 2 pneumonias related to docetaxel).
Conclusions: Nivolumab plus docetaxel has clinical activity in patients with chemotherapy-naïve mCRPC. Safety was consistent with the individual components. These results support further investigation in the ongoing phase III CheckMate 7DX trial.
ClinicalTrials.gov registration: NCT03338790.

1. Introduction

The emergence of immune checkpoint inhibitors targeting the programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) pathway has revolutionised treatment of various advanced cancers. However, although single-agent anti–PD-1/PD-L1 therapies have been shown to improve outcomes for some tumours, they provide suboptimal clinical benefits in unselected patient populations with metastatic castration-resistant prostate cancer (mCRPC) [1–5]. Nevertheless, long-term survival benefits and sustained complete remissions have been reported in patients with mCRPC receiving the cytotoxic T lymphocyte–associated antigen-4 inhibitor ipilimumab [6,7], suggesting that some patients can benefit from checkpoint blockade. A generally accepted explanation for the suboptimal clinical activity of checkpoint inhibitors is that it is because most patients with mCRPC harbour a largely immunosuppressive tumour microenvironment, characterised by low infiltration of CD8+ T cells and increased densities of immunosuppressive cell types, such as neutrophils, monocytic myeloid-derived suppressor cells and T_H17 and T_{reg} cell populations [8–10]. Accordingly, clinical trials are investigating regimens combining anti–PD-1/PD-L1 agents with existing anticancer treatments that have potential to stimulate a more immunoresponsive prostate cancer microenvironment, including inhibitors of distinct immune checkpoint pathways or other systemic anticancer treatments [11–14].

Docetaxel is a currently recommended first-line treatment for mCRPC [15–18]. Although the anticancer activity of docetaxel is typically associated with inhibition of microtubule depolymerisation and related mitotic arrest and tumour cell death [19], there is evidence of additional immunostimulatory effects. Preclinical and clinical studies have shown that taxanes, such as docetaxel, may enhance antitumour immune responses by increasing tumour antigen presentation, promoting production of inflammatory cytokines and/or modifying immune cell populations, most notably the downregulation of immunosuppressive T cells [19–21]. As these immune-related effects might provide a stimulus to switch the prostate tumour microenvironment from immunosuppressive to immunoresponsive, there is a therapeutic rationale for combining anti–PD-1/PD-L1 agents with docetaxel for mCRPC, an approach that appears to be successful in patients with lung cancer [22].

We report results from cohort B of the multicohort, phase II CheckMate 9KD trial, which evaluated the efficacy and safety of the anti–PD-1 inhibitor nivolumab combined with docetaxel in men with chemotherapy-naïve mCRPC.

2. Methods

2.1. Study population

CheckMate 9KD (NCT03338790) is a non-randomised, open-label, multicohort, phase II trial of nivolumab

combined with rucaparib, docetaxel or enzalutamide for mCRPC. Eligible patients were adults with histologically confirmed adenocarcinoma of the prostate with radiologic evidence of M1 metastatic disease, ongoing androgen deprivation therapy with a gonadotropin-releasing hormone analogue or bilateral orchiectomy (confirmed by a testosterone level ≤1.73 nmol/L at screening), documented prostate cancer progression per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (Supplementary Methods 1) and an Eastern Cooperative Oncology Group performance status of 0–1. Patients also had to have sufficient tumour tissue obtained within 5 years before enrolment from a metastatic tumour lesion or primary tumour lesion not previously irradiated. The exclusion criteria included active brain metastases, conditions requiring systemic corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the start of study treatment and prior treatments specifically targeting T-cell co-stimulation or checkpoint pathways.

Patients were assigned to treatment cohorts based on prior therapy received in the castration-resistant setting and eligibility for receipt of immediate chemotherapy (Fig. S1). For assignment to cohort B, patients had to have chemotherapy-naïve mCRPC and be candidates for immediate docetaxel treatment (per the investigator's discretion). Prior treatment with up to 2 novel hormonal therapies (NHTs; i.e. abiraterone, enzalutamide or apalutamide) in the castration-resistant setting was permissible if the last dose was administered >28 days before cohort assignment. Patients who previously received docetaxel or another chemotherapy for mCRPC were excluded, although prior docetaxel treatment for metastatic hormone-sensitive prostate cancer was allowed if ≥ 12 months had elapsed from the last docetaxel dose. Patients with grade ≥2 peripheral neuropathy (per National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) were also excluded from cohort B.

The study was approved by the institutional review board/ethics committee at each site and conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences and Good Clinical Practice, as defined by the International Conference on Harmonisation. All patients provided written informed consent.

2.2. Procedures

Patients in cohort B received a combination of intravenous nivolumab 360 mg and docetaxel 75 mg/m^2 every 3 weeks, with oral prednisone 5 mg twice daily, for a maximum of 10 cycles, followed by nivolumab monotherapy (480 mg every 4 weeks) for up to 2 years from the date of the first nivolumab dose. Oral dexamethasone 8 mg was given as premedication at 12, 3 and 1 h before docetaxel infusion. Treatment could be prematurely discontinued because of disease progression, unacceptable toxicity, withdrawal of consent or the end of the trial, whichever occurred first. If docetaxel was discontinued before cycle 10, nivolumab 360 mg every 3 weeks was administered alone until cycle 10.

2.3. Assessments

The co-primary end-points were objective response rate (ORR; proportion of patients achieving a confirmed complete or partial response as assessed by the investigator using PCWG3 criteria) and prostate-specific antigen (PSA) response rate (PSA_{50}-RR; proportion of patients with a ≥50% PSA decrease from baseline). The secondary end-points included investigator-assessed radiographic progression-free survival (rPFS), time to and duration of objective response, time to PSA progression, overall survival (OS) and safety. PCWG3 criteria were used to assess rPFS, time to and duration of objective response and time to PSA progression.

The preplanned or post hoc exploratory end-points included the proportion of patients with a ≥30% PSA decrease from baseline (PSA_{30}-RR; post hoc), time to and duration of PSA_{50} response (post hoc), and associations between efficacy outcomes and (1) prior NHT in the castration-resistant setting (post hoc), (2) homologous recombination deficiency (HRD) mutational status (preplanned) and (3) tumour mutational burden (TMB; post hoc). HRD and TMB analysis methodology is described in Supplementary Methods 2.

Adverse events (AEs), graded per CTCAE v.4.03, are reported from the first dose of nivolumab plus docetaxel up to 30 days after the last dose of study drug. Immune-mediated AEs (i.e. those consistent with an immune-mediated mechanism or component for which non-inflammatory etiologies, e.g. infection or tumour progression, were ruled out) are reported up to 100 days after the last dose of study drug.

Imaging assessments in cohort B (computed tomography/magnetic resonance imaging and radionuclide bone scans) were performed during screening, every 8 weeks (±1 week) from the first dose to week 24 and then every 12 weeks (±1 week) until disease progression or treatment discontinuation (whichever was later). Objective responses and progressive disease were confirmed by repeat scans. PSA was assessed locally at screening, on day 1 of cycles 1 through 5 and then day 1 of every other treatment cycle starting with cycle 7. PSA responses were confirmed by a second consecutive assessment obtained ≥3 weeks later.

2.4. Statistical analyses

Enrolment of 85 patients was planned for cohort B with sample size calculations based on the precision approach

for the co-primary end-points (Supplementary Methods 3). Efficacy and safety analyses were conducted on the all-treated population (all patients receiving a dose of nivolumab and/or docetaxel). Objective response analyses were conducted on treated patients with baseline measurable disease. PSA response analyses were conducted on treated patients with a baseline and ≥1 postbaseline PSA assessment (PSA-evaluable patients).

ORRs and PSA response rates and corresponding 2-sided exact 95% confidence intervals (CIs) were calculated using Clopper–Pearson methodology [23]. Time to and duration of objective response, time to PSA progression, rPFS and OS were estimated using the Kaplan–Meier method [24]. For rPFS, OS and duration of objective response, median values and corresponding 95% CIs were constructed based on a log–log transformed CI for the survivor function [25].

3. Results

Eighty-four men with mCRPC received nivolumab plus docetaxel (all-treated population). Patient and disease characteristics are shown in Table 1. Most patients (n = 54, 64.3%) had received prior NHT in the castration-resistant setting, mainly enzalutamide (n = 24, 28.6%), abiraterone (n = 17, 20.2%) or both enzalutamide and abiraterone (n = 12, 14.3%). Patient disposition is summarised in Table S1; at data cutoff (17 July 2020), 76 patients (90.5%) had discontinued all study treatments, mostly because of disease progression (n = 50, 59.5%) or study drug toxicity (n = 15, 17.9%). Treatment exposure is described in Table S2. The median duration (range) of therapy was 7.2 (0.0–22.1) months for nivolumab and 5.2 (0.0–7.6) months for docetaxel; the median (range) number of doses received was 11.0 (1–27) and 8.0 (1–10), respectively. The median follow-up was 15.2 months.

Among 45 treated patients with baseline measurable disease, the confirmed ORR (95% CI) was 40.0% (25.7–55.7), with 1 patient (2.2%) achieving a complete response and 17 (37.8%) achieving partial responses (Table 2). The median time to objective response (range) was 2.0 (1.6–7.3) months, and the median response duration (95% CI) was 7.0 (6.4–12.4) months. Among 81 PSA-evaluable patients, the confirmed PSA_{50}-RR (95% CI) was 46.9% (35.7–58.3) and the confirmed PSA_{30}-RR (95% CI) was 58.0% (46.5–68.9; Table 2). In all 84 treated patients, the median rPFS (95% CI) was 9.0 (8.0–11.6) months (Fig. 1A) and the median OS (95% CI) was 18.2 (14.6–20.7) months (Fig. 1B).

In subpopulations with versus without prior NHT, the confirmed ORR (95% CI) was 38.7% (21.8–57.8) versus 42.9% (17.7–71.1) in patients with baseline measurable disease, and the confirmed PSA_{50}-RR and PSA_{30}-RR (95% CI) were 39.6% (26.5–54.0) versus 60.7% (40.6–78.5) and 52.8% (38.6–66.7) versus 67.9% (47.6–84.1), respectively, in PSA-evaluable patients.

Table 1
Patient demographic and disease characteristics.

Characteristic	All treated patients (N = 84)
Median age (range), years	71 (53–88)
Age category, n (%)	
<70 years	39 (46.4)
≥70 years	45 (53.6)
Race, n (%)	
White	70 (83.3)
Black or African American	8 (9.5)
Other	6 (7.1)
Geographic region, n (%)	
United States	29 (34.5)
Europe	18 (21.4)
Rest of the world[a]	37 (44.0)
ECOG performance status, n %	
0	36 (42.9)
1	48 (57.1)
Gleason score, n (%)	
≤7	33 (39.3)
>7	49 (58.3)
Not reported	2 (2.4)
Median time since diagnosis (range), years	4.6 (0.3–47.7)
Bone lesions, n (%)	
0	9 (10.7)
1–4	23 (27.4)
>4	52 (61.9)
Visceral metastases, n (%)	
Yes	23 (27.4)
No	59 (70.2)
Not reported	2 (2.4)
Measurable disease, n (%)	45 (53.6)
Average daily worst pain intensity, n (%)	
<4	52 (61.9)
≥4	28 (33.3)
Not reported	4 (4.8)
Median PSA (range), ng/mL[b]	49.5 (1.2–1085.0)
PD-L1 expression, n (%)	
<1%	47 (56.0)
≥1%	4 (4.8)
Not reported	33 (39.3)
Haemoglobin, n (%)	
<110 g/L	12 (14.3)
≥110 g/L	71 (84.5)
Not reported	1 (1.2)
Alkaline phosphatase, n (%)	
<1.5 × ULN	57 (67.9)
≥1.5 × ULN	26 (31.0)
Not reported	1 (1.2)
Lactate dehydrogenase, n (%)	
≤ULN	51 (60.7)
>ULN	31 (36.9)
Not reported	2 (2.4)
Prior cancer surgery, n (%)	40 (47.6)
Prior radiotherapy, n (%)	54 (64.3)
Prior NHT in castration-resistant setting, n (%)	
Any NHT	54 (64.3)
Enzalutamide only	24 (28.6)
Abiraterone only	17 (20.2)
Enzalutamide and abiraterone	12 (14.3)
Apalutamide only	1 (1.2)

ECOG, Eastern Cooperative Oncology Group; NHT, novel hormonal therapy; PD-L1, programmed death ligand 1; PSA, prostate-specific antigen; ULN, upper limit of normal.
[a] Represents Australia, Canada and South America.
[b] Based on 81 patients with available baseline PSA data.

Table 2
Objective and PSA response outcomes in all treated patients.

Objective responses[a]	Evaluable patients (n = 45)[b]
Confirmed ORR (95% CI), %	40.0 (25.7–55.7)
BOR, n (%)	
Complete response	1 (2.2)[c]
Partial response	17 (37.8)
Stable disease	24 (53.3)
Progressive disease	3 (6.7)
Median time to objective response (range), months	2.0 (1.6–7.3)
Median duration of objective response (95% CI), months	7.0 (6.4–12.4)
PSA responses[d]	**Evaluable patients (n = 81)[e]**
Confirmed or unconfirmed PSA_{50}-RR (95% CI), %	53.1 (41.7–64.3)
Confirmed PSA_{50}-RR (95% CI), %	46.9 (35.7–58.3)
Median time to confirmed PSA_{50} response (range), months	1.4 (0.6–7.1)
Median duration of confirmed PSA_{50} response (95% CI), months	8.4 (6.0–9.5)
Confirmed or unconfirmed PSA_{30}-RR (95% CI), %	64.2 (52.8–74.6)
Confirmed PSA_{30}-RR (95% CI), %	58.0 (46.5–68.9)
Median time to PSA progression (95% CI), months[f]	8.7 (7.3–10.4)

BOR, best overall response; CI, confidence interval; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA_{30}-RR, ≥30% decrease in PSA from baseline; PSA_{50}-RR, ≥50% decrease in PSA from baseline.
[a] Confirmed complete or partial response per PCWG3.
[b] Patients with measurable disease at baseline.
[c] The patient achieving a complete response per PCWG3 also achieved a substantial decline in PSA (baseline, 6.2 ng/mL; day 22, 0.4 ng/mL with PSA maintained <1 ng/mL through day 547) and a rapid reduction in diameter of the target lymph node lesion (screening, 22 mm; week 9, 11 mm; week 48, 0 mm).
[d] A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50% (PSA_{50}) or ≥30% (PSA_{30}); a second consecutive value obtained ≥3 weeks later was required for confirmation of PSA responses.
[e] Patients with a baseline and ≥1 postbaseline PSA assessment.
[f] PSA progression was defined as the date of an increase of ≥25% or an absolute increase of ≥2 ng/mL from the PSA nadir.

The median rPFS (95% CI) was 8.5 (7.5–10.8) versus 12.0 (6.2–18.2) months, and the median OS (95% CI) was 16.2 (13.5–18.3) months versus not reached (9.9–not estimable; Table 3, Fig. 2A–B). Maximum changes in tumour size and PSA from baseline based on prior NHT are displayed in Fig. S2.

In subpopulations with HRD-negative/not evaluable tumours versus HRD-positive tumours, the confirmed ORR (95% CI) was 42.3% (23.4–63.1) versus 36.8% (16.3–61.6) in patients with baseline measurable disease, and the confirmed PSA_{50}-RR and PSA_{30}-RR (95% CI) were 44.7% (30.2–59.9) versus 50.0% (32.4–67.6) and 63.8% (48.5–77.3) versus 50.0% (32.4–67.6), respectively, in PSA-evaluable patients. The median rPFS (95% CI) was 8.3 (5.7–11.5) versus 9.8 (8.3–12.9) months, and the median OS (95% CI) was 18.2 (13.5–not estimable) versus 18.3 (13.0–not estimable) months (Table 3, Fig. 2C–D).

In subpopulations with TMB <10 versus ≥10 mutations/Mb, the confirmed ORR (95% CI) was 50.0% (29.1–70.9) versus 38.5% (13.9–68.4) in patients with baseline measurable disease, and the confirmed PSA_{50}-RR and PSA_{30}-RR (95% CI) were 52.2% (36.9–67.1) versus 31.6% (12.6–56.6) and 58.7% (43.2–73.0) versus 52.6 (28.9–75.6), respectively, in PSA-evaluable patients. The median rPFS (95% CI) was 9.8 (8.2–12.0) versus 9.0 (6.2–12.9) months, and the median OS (95% CI) was 17.3 (13.0–not estimable) versus 15.7 (6.8–not estimable) months (Table 3, Fig. 2E–F). Efficacy outcomes based on median TMB are shown in Table S3.

Any-grade treatment-related AEs occurred in 95.2% of all treated patients, most frequently fatigue (39.3%), diarrhoea (35.7%) and alopecia (34.5%; Table 4). Grade 3-4 treatment-related AEs occurred in 47.6% of patients, most commonly neutropenia (16.7%). Any-grade and grade 3-4 treatment-related serious AEs were reported in 27.4% and 26.2% of all treated patients, respectively, with the most frequent event being pneumonitis (6.0% and 4.8%). Any-grade and grade 3-4 treatment-related AEs led to discontinuation of one or both study drugs

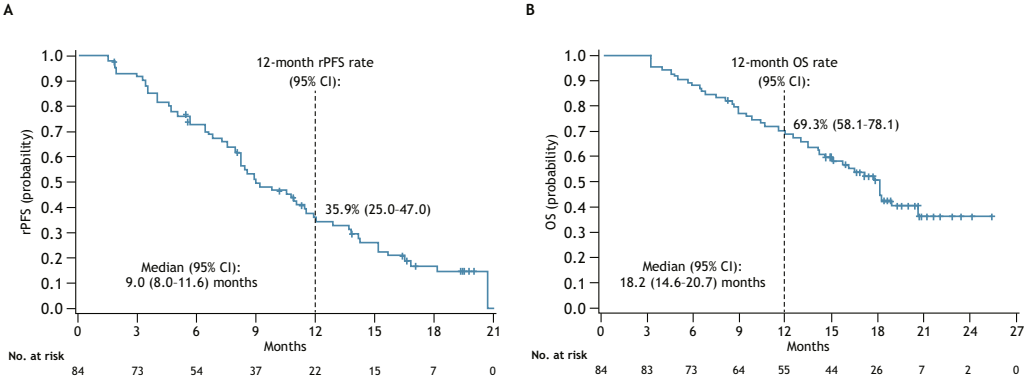

Fig. 1. Kaplan–Meier plots of (A) rPFS and (B) OS in all treated patients. CI, confidence interval; OS, overall survival; rPFS, radiographic progression-free survival.

Table 3
Objective and PSA response outcomes based on prior NHT, HRD and TMB status.

Objective responses[a]	Prior NHT status		HRD status		TMB status	
	Prior	No prior	Negative/Not evaluable	Positive	<10 mut/Mb	≥10 mut/Mb
Evaluable patients[b]	31	14	26	19	24	13
ORR (95% CI), %	38.7 (21.8–57.8)	42.9 (17.7–71.1)	42.3 (23.4–63.1)	36.8 (16.3–61.6)	50.0 (29.1–70.9)	38.5 (13.9–68.4)
BOR, n (%)						
Complete response	1 (3.2)	0	0	1 (5.3)	0	1 (7.7)
Partial response	11 (35.5)	6 (42.9)	11 (42.3)	6 (31.6)	12 (50.0)	4 (30.8)
Stable disease	17 (54.8)	7 (50.0)	14 (53.8)	10 (52.6)	11 (45.8)	7 (53.8)
Progressive disease	2 (6.5)	1 (7.1)	1 (3.8)	2 (10.5)	1 (4.2)	1 (7.7)
PSA responses[c]	Prior	No prior	Negative/Not evaluable	Positive	<10 mut/Mb	≥10 mut/Mb
Evaluable patients[d]	53	28	47	34	46	19
PSA_{50}-RR (95% CI), %	39.6 (26.5–54.0)	60.7 (40.6–78.5)	44.7 (30.2–59.9)	50.0 (32.4–67.6)	52.2 (36.9–67.1)	31.6 (12.6–56.6)
PSA_{30}-RR (95% CI), %	52.8 (38.6–66.7)	67.9 (47.6–84.1)	63.8 (48.5–77.3)	50.0 (32.4–67.6)	58.7 (43.2–73.0)	52.6 (28.9–75.6)

BOR, best overall response; CI, confidence interval; HRD, homologous recombination deficiency; mut, mutations; NHT, novel hormonal therapy; ORR, objective response rate; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen; PSA_{30}-RR, ≥30% decrease in PSA from baseline; PSA_{50}-RR, ≥50% decrease in PSA from baseline; TMB, tumour mutation burden.

[a] Confirmed complete or partial response per PCWG3.

[b] Patients with measurable disease at baseline and available data on NHT, HRD or TMB status (as applicable).

[c] A decrease in PSA from baseline to the lowest postbaseline PSA result of ≥50% (PSA_{50}) or ≥30% (PSA_{30}); a second consecutive value obtained ≥3 weeks later was required for confirmation of PSA response.

[d] Patients with a baseline and ≥1 postbaseline PSA assessment and available data on NHT, HRD or TMB status (as applicable).

in 29.8% and 14.3% of all treated patients, respectively, with the most frequent event leading to discontinuation being pneumonitis (in 7.1% and 4.8%, respectively; Table 4). The most common any-grade immune-mediated AEs were rash (10.7%), pneumonitis (9.5%) and hypothyroidism (6.0%); the most common grade 3-4 immune-mediated AE was pneumonitis (4.8%; Table S4).

There were 3 on-study deaths related to study treatment; 1 case of pneumonitis was considered related to nivolumab, and 2 cases of pneumonia were considered related to docetaxel (details in Table S5).

4. Discussion

Based on the potential for immunostimulatory effects of docetaxel to promote a more immunoresponsive prostate tumour microenvironment, cohort B of the phase II CheckMate 9KD trial assessed the combination of nivolumab plus docetaxel for mCRPC. Here, the combination showed antitumour activity in men with chemotherapy-naïve mCRPC with more than a third of treated patients achieving a confirmed objective response and almost half achieving a ≥50% PSA decline from baseline.

Because prior treatment with NHT represents an additional line of therapy, there was an expectation that patients not previously receiving NHT would show better responses to nivolumab plus docetaxel, as they are receiving therapy at an earlier timepoint in their disease course. Indeed, in our study, ORRs and PSA response rates were higher and rPFS and OS were longer among patients without prior NHT. Nevertheless, clinical activity of nivolumab plus docetaxel was observed among patients who had received prior NHT in the castration-resistant setting, with an ORR of 39%, a PSA_{50}-RR of 40% and a median OS of 16.2 months. This aligns with a recent study of pembrolizumab plus docetaxel for patients with mCRPC previously exposed to either abiraterone or enzalutamide (but not both) reporting an ORR of 23%, a PSA_{50}-RR of 34% and a median OS of 20.2 months [26].

A critical aspect of evaluating combination therapy is determining its benefit over the individual components. Without head-to-head studies, this can only be surmised in the context of findings from other clinical studies. However, cross-study comparison should be treated with caution because of the potential influence of study design and patient population differences on efficacy outcomes. For example, multiple studies of docetaxel alone for mCRPC have reported ORRs ranging from 12% to 36%, PSA_{50}-RRs ranging from 27% to 68% and OS medians ranging from 18.9 to 24.3 months [15,27–32]. It is also noteworthy that most of these studies included either no or very small numbers of patients with prior NHT, a characteristic that has been shown in this study and elsewhere [31,33,34], to influence efficacy outcomes. Moreover, the studies also varied in other design features, such as whether PSA responses were confirmed, and the number of allowable chemotherapy cycles, which has also been shown to impact outcomes with docetaxel [35].

Here, we found no clear association between HRD status or TMB and response to nivolumab plus docetaxel. Previously, several small studies have suggested improved response to single-agent or combination immunotherapy among patients with mCRPC harbouring DNA repair mutations or with 'high' TMB

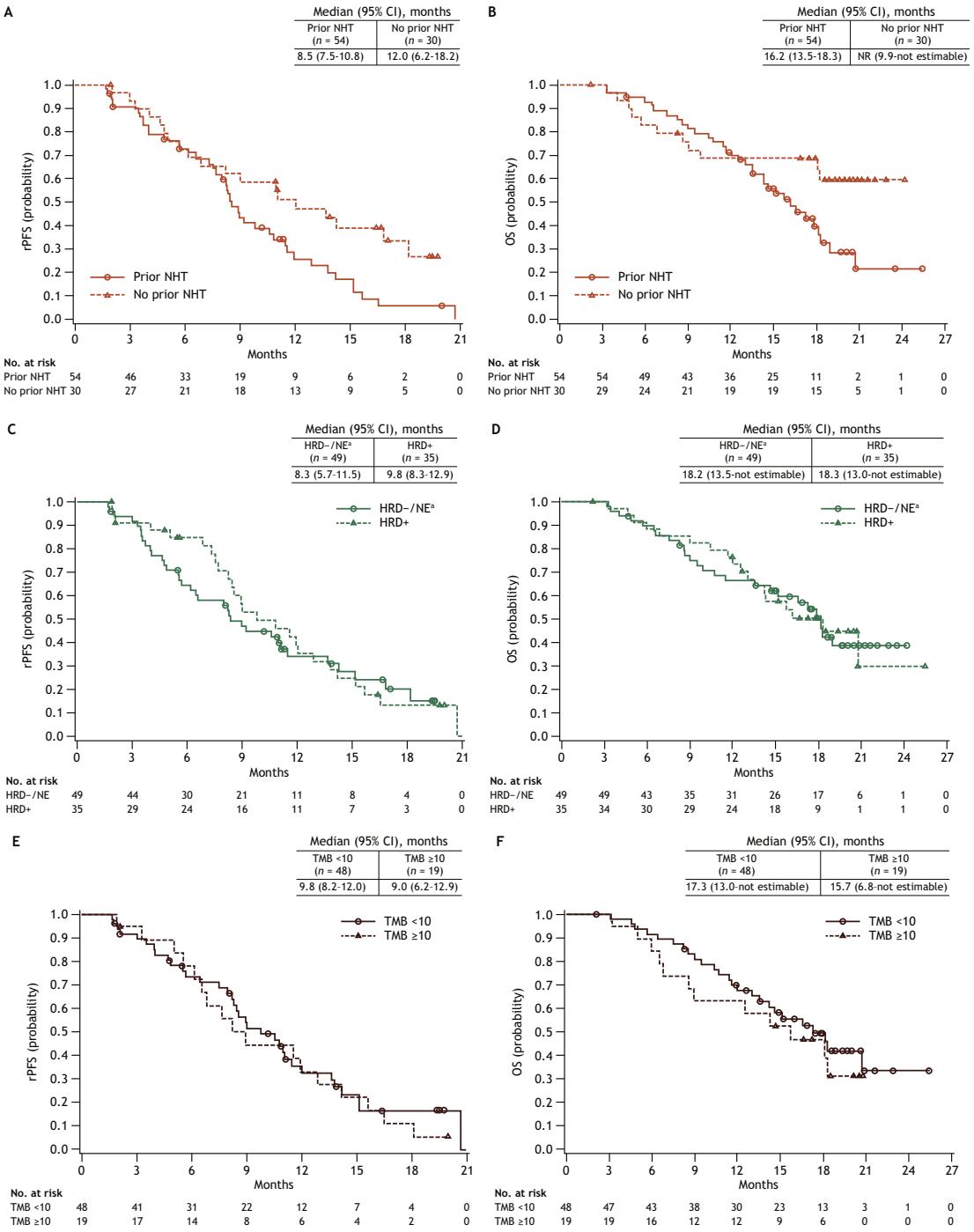

Fig. 2. Kaplan–Meier plots of rPFS and OS based on prior NHT (A and B), HRD (C and D) or TMB (E and F) status. CI, confidence interval; HRD, homologous recombination deficiency; NE, not evaluable; NHT, novel hormonal therapy; NR, not reached; OS, overall survival; rPFS, radiographic progression-free survival; TMB, tumour mutational burden. [a] Includes 46 patients confirmed with HRD-negative tumours and 3 patients not evaluable for HRD.

Table 4
Treatment-related AEs in all treated patients ($N = 84$).

Treatment-related AEs, *n* (%)[a]	Any grade	Grade 3-4
Any treatment-related AE	80 (95.2)	40 (47.6)
Fatigue	33 (39.3)	4 (4.8)
Diarrhoea	30 (35.7)	4 (4.8)
Alopecia	29 (34.5)	0
Nausea	25 (29.8)	1 (1.2)
Anaemia	20 (23.8)	3 (3.6)
Peripheral neuropathy	20 (23.8)	0
Decreased appetite	16 (19.0)	0
Neutropenia	15 (17.9)	14 (16.7)
Rash	15 (17.9)	2 (2.4)
Peripheral oedema	15 (17.9)	0
Asthenia	12 (14.3)	3 (3.6)
Dysgeusia	12 (14.3)	0
Pneumonitis	11 (13.1)	4 (4.8)
Dyspnoea	11 (13.1)	2 (2.4)
Constipation	10 (11.9)	1 (1.2)
Cough	9 (10.7)	1 (1.2)
Dizziness	8 (9.5)	0
Neutrophil count decreased	7 (8.3)	4 (4.8)
Chills	7 (8.3)	0
Nail discolouration	7 (8.3)	0
Pneumonia	5 (6.0)	4 (4.8)
Vomiting	5 (6.0)	0
Febrile neutropenia	4 (4.8)	4 (4.8)
Treatment-related serious AEs, *n* (%)[b]	Any grade	Grade 3-4
Any treatment-related serious AE	23 (27.4)	22 (26.2)
Pneumonitis	5 (6.0)	4 (4.8)
Pneumonia	4 (4.8)	4 (4.8)
Febrile neutropenia	4 (4.8)	4 (4.8)
Diarrhoea	3 (3.6)	3 (3.6)
Neutropenia	2 (2.4)	2 (2.4)
Treatment-related AEs leading to discontinuation, *n* (%)[c]	Any grade	Grade 3-4
Any treatment-related AE leading to discontinuation	25 (29.8)	12 (14.3)
Pneumonitis	6 (7.1)	4 (4.8)
Fatigue	5 (6.0)	0
Peripheral neuropathy	5 (6.0)	0
Pneumonia	3 (3.6)	2 (2.4)
Asthenia	2 (2.4)	1 (1.2)

AE, adverse event.
[a] Includes individual any-grade treatment-related AEs occurring in >5% of all treated patients and/or grade 3–4 treatment-related AEs occurring in >2% of all treated patients.
[b] Includes individual any-grade treatment-related serious AEs occurring in >2% of all treated patients.
[c] Represents a treatment-related AE that led to permanent discontinuation of nivolumab and/or docetaxel; includes individual any-grade treatment-related AEs occurring in >2% of all treated patients.

[4,11,12]. However, based on the preliminary nature of these data, and other recent studies indicating that the effect of DNA repair mutations and TMB on response to immune checkpoint inhibitors is tumour type–dependent [36,37], it remains unclear how these mutational factors influence outcomes in immunotherapy-treated patients with mCRPC. In addition, the effect of TMB on the efficacy of docetaxel monotherapy is unknown. Thus, larger prospective studies are needed to adequately investigate the impact of DNA repair mutations and TMB, as well as other possible biomarkers such as microsatellite instability-high disease and cyclin-dependent kinase 12 (*CDK12*) alterations, on response to nivolumab plus docetaxel in men with mCRPC.

Safety of nivolumab plus docetaxel was generally as expected based on the types of AEs previously observed in studies of the single components [15,32,38,39]. Nevertheless, the rate of treatment-related pneumonitis was higher than anticipated based on prior studies of nivolumab and docetaxel alone [27,40], and 3 treatment-related deaths were associated with pneumonitis or pneumonia. Of note, 2 patients also died of treatment-related pneumonitis in the recent study of pembrolizumab plus docetaxel for post-NHT mCRPC [26]. Close monitoring and careful management of immune-mediated AEs, in particular pneumonitis-related events, will likely be important in future trials combining anti–PD-1 agents and docetaxel for prostate cancer, including the phase III CheckMate 7DX trial (NCT04100018), which will prospectively assess nivolumab plus docetaxel versus docetaxel alone for chemotherapy-naïve mCRPC.

5. Conclusion

The final analysis from cohort B of CheckMate 9KD showed clinical activity for nivolumab plus docetaxel in men with chemotherapy-naïve mCRPC. Moreover, the antitumour effects of nivolumab plus docetaxel were observed regardless of prior NHT, HRD status or TMB. Although no new safety signals were observed with nivolumab plus docetaxel, monitoring of immune-mediated AEs will be important for future clinical trials of this combination in the mCRPC setting.

Author contribution statement

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: KF reports consulting or advisory fees (institutional) from Janssen Oncology, Astellas Pharma, Sanofi, AstraZeneca, ESSA, and Amgen; consulting or advisory fees (personal) from Bayer, Orion Pharma GmbH, CureVac, Bristol Myers Squibb (BMS), and Clovis Oncology; travel accommodations, expenses from Janssen and MSD; honoraria (institutional) from Janssen, Sanofi, and Astellas Pharma; and honoraria (personal) from Bayer.

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Appendix A. Supplementary data

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