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Platinum Priority – Prostate Cancer

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Pembrolizumab Plus Docetaxel and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort B Study

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Abstract

Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) frequently receive docetaxel after they develop resistance to abiraterone or enzalutamide and need more efficacious treatments.
Objective: To evaluate the efficacy and safety of pembrolizumab plus docetaxel and prednisone in patients with mCRPC.

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Design, setting, and participants: The trial included patients with mCRPC in the phase 1b/2 KEYNOTE-365 cohort B study who were chemotherapy naïve and who experienced failure of or were intolerant to ≥4 wk of abiraterone or enzalutamide for mCRPC with progressive disease within 6 mo of screening.
Intervention: Pembrolizumab 200 mg intravenously (IV) every 3 wk (Q3W), docetaxel 75 mg/m^2 IV Q3W, and prednisone 5 mg orally twice daily.
Outcome measurements and statistical analysis: The primary endpoints were safety, the prostate-specific antigen (PSA) response rate, and the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR). Secondary endpoints included time to PSA progression; the disease control rate (DCR) and duration of response (DOR) according to RECIST v1.1 by BICR; ORR, DCR, DOR, and radiographic progression-free survival (rPFS) according to Prostate Cancer Working Group 3–modified RECIST v1.1 by BICR; and overall survival (OS).
Results and limitations: Among 104 treated patients, 52 had measurable disease. The median time from allocation to data cutoff (July 9, 2020) was 32.4 mo, during which 101 patients discontinued treatment, 81 (78%) for disease progression. The confirmed PSA response rate was 34% and the confirmed ORR (RECIST v1.1) was 23%. Median rPFS and OS were 8.5 mo and 20.2 mo, respectively. Treatment-related adverse events (TRAEs) occurred in 100 patients (96%). Grade 3–5 TRAEs occurred in 46 patients (44%). Seven AE-related deaths (6.7%) occurred (2 due to treatment-related pneumonitis). Limitations of the study include the single-arm design and small sample size.
Conclusions: Pembrolizumab plus docetaxel and prednisone demonstrated antitumor activity in chemotherapy-naïve naive patients with mCRPC treated with abiraterone or enzalutamide for mCRPC. Safety was consistent with profiles for the individual agents. Further investigation is warranted.
Patient summary: We evaluated the efficacy and safety of the anti-PD-1 antibody pembrolizumab combined with the chemotherapy drug docetaxel and the steroid prednisone for patients with metastatic prostate cancer resistant to androgen deprivation therapy, and who never received chemotherapy. The combination showed antitumor activity and manageable safety in this patient population.
This trial is registered on ClinicalTrials.gov as NCT02861573.

1. Introduction

Despite significant advances in the treatment of prostate cancer, the primary systemic treatment for regional or metastatic prostate cancer is androgen deprivation therapy (ADT) [1]. Most patients with metastatic disease develop resistance to ADT within 1–2 yr and progress to metastatic castration-resistant prostate cancer (mCRPC) [2]. Several treatment options show a survival benefit after development of mCRPC—including abiraterone [3], enzalutamide [4], docetaxel [5], cabazitaxel [6], sipuleucel-T [7], and radium-223 [8]—but are not curative. Next-generation hormonal agents (NHAs) such as abiraterone and enzalutamide are often used following disease progression after ADT, but there is no consensus regarding the optimal sequence for therapy after progression. Docetaxel is a recommended treatment after initial progression on abiraterone or enzalutamide despite the lack of prospective data for docetaxel after NHA therapy [1]. To date, docetaxel combination regimens have not shown a survival benefit over sequential monotherapies with docetaxel [1]. With a 5-yr survival rate estimated at 30% for patients with distant metastases [9,10], there is a need for therapies that prolong survival.

The tumor microenvironment is immunosuppressive in patients with prostate cancer, and therefore restoring the T-cell antitumor response via programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) blockade is a promising treatment approach [11,12]. Elevated expression of PD-L1 on tumor-infiltrating T cells has been associated with disease progression in prostate cancer [13]. Furthermore, a recent immunohistochemical study showed that metastases from CRPC tumors in patients previously treated with NHAs had increased PD-L1 expression and immunoreactivity [14]. Pembrolizumab is a highly selective humanized monoclonal antibody that blocks interaction between PD-1 and its ligands, PD-L1 and PD-L2, and is approved for the treatment of multiple tumor types [15]. In the phase 2 KEYNOTE-199 trial, pembrolizumab monotherapy showed antitumor activity with manageable safety in patients with mCRPC previously treated with docetaxel and one or more targeted endocrine therapies [16]. Preclinical studies have shown that many chemotherapeutic agents, including taxanes such as docetaxel, can have immunostimulatory effects [17]. Combining immunotherapy and standard chemotherapy may therefore enhance antitumor activity.

The phase 1b/2 KEYNOTE-365 trial (NCT02861573) evaluated the safety, tolerability, and efficacy of pembrolizumab combination therapy in patients with mCRPC. We describe the results for cohort B, which included chemotherapy-naïve patients with mCRPC who experienced disease progression

on abiraterone or enzalutamide for mCRPC and who were treated with the combination of pembrolizumab, docetaxel, and prednisone.

2. Patients and methods

2.1. Study design and patients

KEYNOTE-365 is a multicohort, nonrandomized, multicenter, open-label, phase 1b/2 trial. Patients in eight countries (Australia, Canada, France, Germany, New Zealand, Spain, UK, and USA) were enrolled in cohort B. The trial was conducted in accordance with good clinical practice and the Declaration of Helsinki. The protocol and its amendments were approved by the appropriate ethics body at each participating institution. All patients provided written informed consent.

Key eligibility criteria included age ≥18 yr; histologically or cytologically confirmed adenocarcinoma of the prostate without small-cell histology; disease that progressed within 6 mo before screening (prostate-specific antigen [PSA] progression or radiologic bone/soft tissue progression); Eastern Cooperative Oncology Group performance status score of 0 or 1; received ≥4 wk of treatment with either abiraterone or enzalutamide (but not both) for mCRPC and with treatment failure or intolerance to the drug; no previous chemotherapy; and serum testosterone level <50 ng/dL. The full inclusion and exclusion criteria are listed in the Supplementary material.

Pembrolizumab 200 mg was administered intravenously (IV) every 3 wk (Q3W) with docetaxel 75 mg/m^2 IV Q3W and prednisone 5 mg orally twice daily. Pembrolizumab was administered for up to 35 cycles (~2 yr), and docetaxel was administered for up to ten cycles.

2.2. Assessments and endpoints

On-study computed tomography or magnetic resonance imaging and radionuclide bone imaging were performed every 9 wk from the date of allocation through week 54, and then every 12 wk thereafter. The response and radiographic progression for soft tissue lesions were assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and radiographic progression for bone lesions was determined according to Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1. Imaging continued until confirmed disease progression, the start of a new anticancer treatment, withdrawal of consent, or death, whichever occurred first. PSA was assessed by a central laboratory at screening and every 3 wk after allocation. Follow-up time began at allocation. PD-L1 positivity was defined as a combined positive score (CPS) ≥1, where CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Adverse events (AEs) were monitored throughout the study through 30 d after the last dose of trial treatment (90 d for serious AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs were determined by the sponsor on the basis of a list of terms specified by the sponsor as potentially associated with immunologic causes.

Primary efficacy endpoints included the PSA response (PSA reduction of ≥50% from baseline, measured twice ≥3 wk apart) and the objective response rate (ORR; complete response [CR] or partial response [PR]) according to RECIST v1.1 as assessed by blinded independent central review (BICR). The primary safety objective was to characterize the safety and tolerability. Secondary endpoints included time to PSA progression; ORR according to PCWG3-modified RECIST v1.1 by BICR; the disease control rate (DCR; CR, PR, stable disease [SD] or non-CR/non-progressive disease [PD] ≥6 mo) and the duration of response (DOR) according to RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR; radiographic progression-free survival (rPFS) according to PCWG3-modified RECIST v1.1 by BICR; and overall survival (OS).

2.3. Statistical considerations

Efficacy and safety populations included all patients who received at least one dose of study treatment (all patients as treated [APaT]). APaT for ORR included only patients with measurable disease at baseline; APaT for DOR included only patients with an objective response. The Clopper-Pearson method was used to provide point estimates and 95% confidence intervals (CIs) for the PSA response rate, ORR, and DCR. The Kaplan-Meier method was used to provide median point estimates and 95% CIs for DOR, time to PSA progression, rPFS, and OS.

Safety and tolerability were assessed via clinical review of all relevant parameters, including AEs, laboratory tests, and vital signs. Counts and percentages for AEs are provided.

Table 1 – Patient demographics and baseline characteristics for the 104 patients treated with pembrolizumab + docetaxel + prednisone

Parameter	Result
Median age, yr (interquartile range)	68 (64–74)
Age ≥65 yr, *n* (%)	77 (74)
Race, *n* (%)	
White	79 (76)
All others	9 (8.7)
Unknown	16 (15)
Geographic region of enrolling site, *n* (%)	
North America	41 (39)
Europe	54 (52)
Rest of the world	9 (8.7)
Eastern Cooperative Oncology Group performance status, *n* (%)	
0	56 (54)
1	48 (46)
Median prostate-specific antigen, ng/mL (interquartile range)	44.1 (17.1–131.4)
PD-L1 status, *n* (%)	
Positive[a]	24 (23)
Negative	76 (73)
Unknown	4 (3.8)
Disease measurable according to RECIST v1.1, *n* (%)	52 (50)
Median baseline tumor size, mm (interquartile range) [b]	49.9 (26.9–73.8)
Visceral disease, *n* (%) [c]	
With liver	8 (7.7)
Without liver	18 (17)
No visceral disease	78 (75)
Metastatic staging, *n* (%)	
M1	61 (59)
M1A	4 (3.8)
M1B	34 (33)
M1C	5 (4.8)
History of brain metastases, *n* (%)	
No	101 (97)
Unknown	3 (2.9)
Previous use of abiraterone/enzalutamide, *n* (%)	
Abiraterone only	51 (49)
Enzalutamide only	52 (50)
Abiraterone and enzalutamide	1 (1.0)

RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
[a] PD-L1 positivity was defined as a combined positive score (CPS) ≥1. CPS was calculated as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.
[b] Assessed by blinded independent central review according to RECIST v1.1.
[c] Soft tissue (not in brain, bone, or lymph nodes).

3. Results

3.1. Disposition, demographics, and exposure

As of July 9, 2020, cohort B enrolled 105 patients; 104 patients whose median age was 68.0 yr (interquartile range [IQR] 64–74) with median PSA of 44.1 ng/mL (IQR 17.1–131.4) were treated (Table 1). Median time from allocation to data cutoff was 32.4 mo (IQR 12.2–27.8). At data cutoff, 101 patients (97%) had discontinued treatment (Supplementary Fig. 1). Among those patients, 81 (78%) discontinued because of disease progression and 15 (14%) because of AEs. Patients received a median of 12 cycles (IQR 7.5–15) of pembrolizumab, and 8.5 cycles (IQR 6–10) of docetaxel. All treated patients received at least two cycles of both treatments; 65 (63%) received at least ten cycles of pembrolizumab and 86 (83%) received at least six cycles of docetaxel. The median duration on therapy, defined as the time between the first dose date and the last dose date, was 7.7 mo (IQR 4.8–9.7).

3.2. Efficacy

The confirmed PSA response rate in patients with a baseline PSA measurement was 34% (35/103) for the total population and 27% (14/51) for patients with RECIST-measurable disease. Seventy-six patients (74%) exhibited any reduction in PSA from baseline, and 45 patients (44%) experienced a PSA reduction of ≥50% from baseline (Fig. 1A). Of 24 patients with PD-L1–positive tumors, 16 (67%) experienced a reduction in PSA from baseline and nine (38%) experienced a reduction of ≥50%. Overall, 56/75 patients (75%) with PD-L1–negative tumors experienced a reduction in PSA from baseline, whereas 35 patients (47%) experienced a reduction of ≥50%. The median time to PSA progression was 29.3 wk (95% CI 21–32; Fig. 1B). PSA response rates were generally consistent across subgroups (Supplementary Fig. 2A).

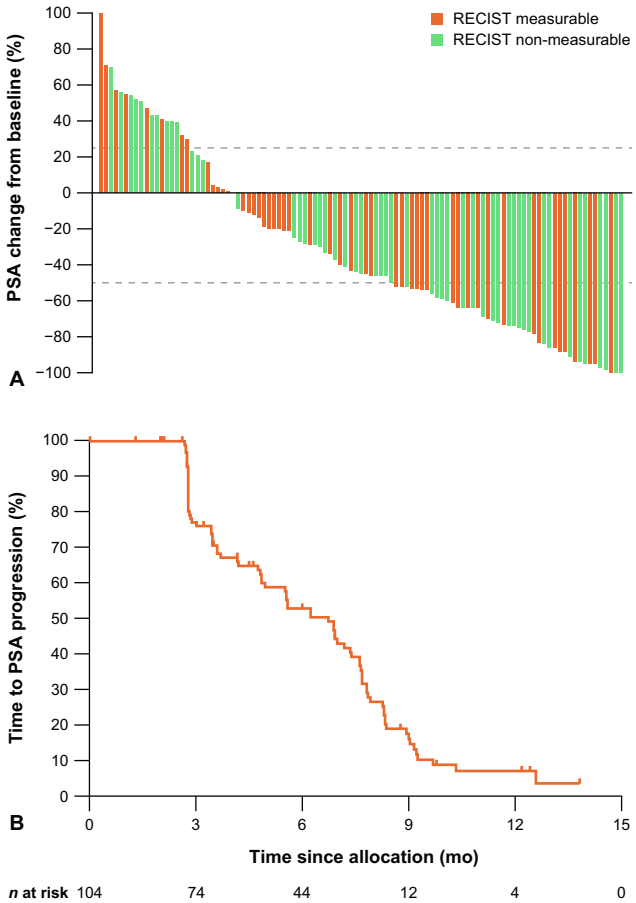

Fig. 1 – (A) Percentage PSA change from baseline (confirmed and unconfirmed; one patient did not have a baseline PSA measurement). (B) Kaplan-Meier estimate of time to PSA progression. PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

The confirmed ORR for patients with RECIST-measurable disease was 23% (CR, *n* = 0; PR, *n* = 12; Table 2). DCR was 54% for the total population by BICR according to RECIST v1.1. ORRs and DCRs were largely similar between subgroups (Supplementary Fig. 2B,C). Forty-seven of 52 patients (90%) experienced reductions in target lesion size from baseline, and 22 patients (42%) experienced reductions of >30% by BICR according to RECIST v1.1 (Fig. 2A). BICR assessment according to PCWG3-modified RECIST v1.1 revealed a DCR of 68% overall and a confirmed ORR of 33% for patients with measurable disease (Supplementary Table 1). For the 12 patients with a response, the estimated median DOR by BICR according to RECIST v1.1 was 6.3 mo (range 3.4–9.0+), and eight patients (67%) had a response duration ≥6 mo according to Kaplan-Meier estimates (Fig. 2B,C). BICR assessment according to PCWG3-modified RECIST v1.1 revealed a median DOR of 6.8 mo (range 3.4–10.4), and nine patients (62%) had a response duration ≥6 mo. Median rPFS was 8.5 mo (95% CI 8.3–10); the 6-mo rPFS rate was 77% and the 12-mo rPFS rate was 26% (Fig. 3A). Median OS was 20.2 mo (95% CI 17–24); the 6-mo OS rate was 96% and the 12-mo OS rate was 76% (Fig. 3B).

3.3. Safety

Treatment-related AEs (TRAEs) attributed by the investigator occurred in 100 patients (96%) (Supplementary Table 2).

Table 2 – Confirmed best response by blinded independent central review according to RECIST v1.1

Parameter	RECIST-MD (*n* = 52)	RECIST-NMD (*n* = 52)	Total (*n* = 104)
Objective response rate, % (95% CI)	23 (13–37)	NA	NA
Disease control rate, % (95% CI) [a]	52 (38–66)	56 (41–70)	54 (44–64)
Best response, *n* (%)			
CR	0 (0)	NA	NA
PR	12 (23)	NA	NA
SD of any duration	26 (50)	0 (0)	26 (25)
Non-CR/non-PD	0 (0)	41 (79)	41 (39)
SD or non-CR/non-PD ≥6 mo	15 (29)	29 (56)	44 (42)
PD	14 (27)	11 (21)	25 (24)

CI = confidence interval; CR = complete response; MD = measurable disease; NA = not applicable; NMD = non-measurable disease; PD = progressive disease; PR = partial response; SD = stable disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.
[a] Disease control rate defined as CR + PR + SD or non-CR/non-PD ≥6 mo.

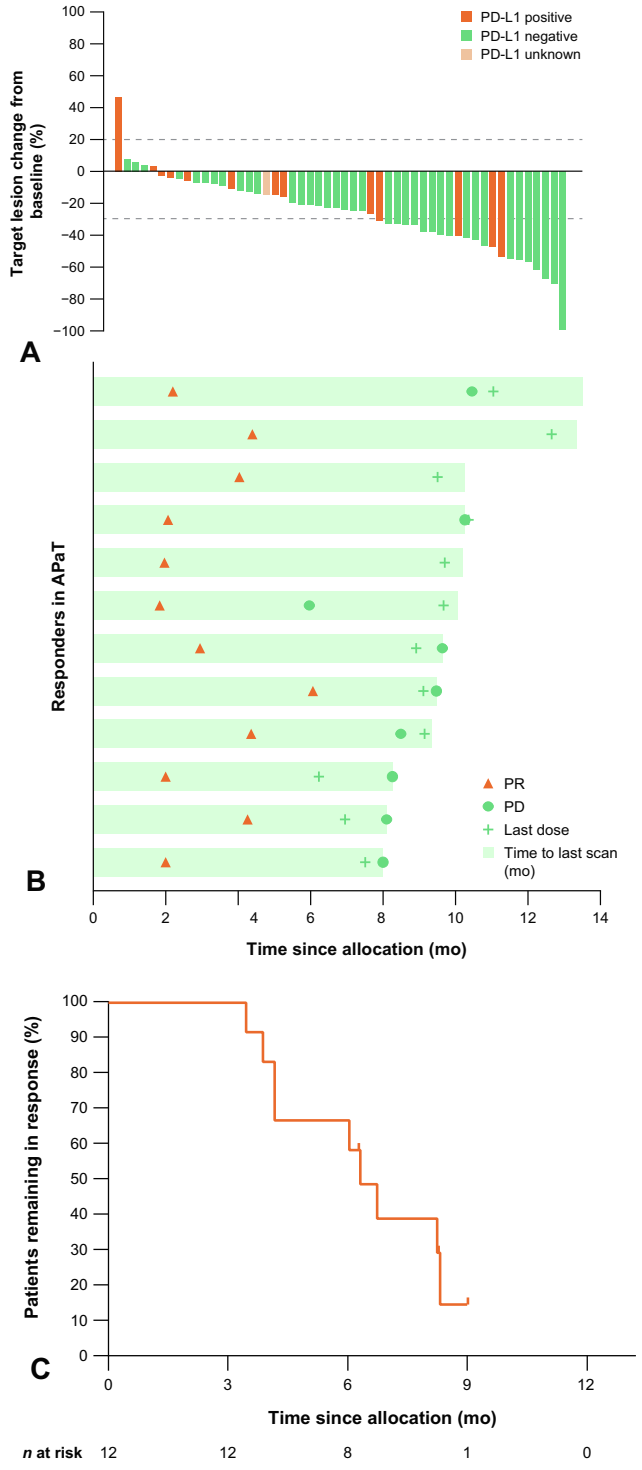

Fig. 2 – (A) Target lesion change from baseline (confirmed and unconfirmed), (B) time to response for responders by BICR according to RECIST version 1.1, and (C) Kaplan-Meier estimate of the duration of response for responders by BICR according to RECIST version 1.1. APaT = all patients as treated; BICR = blinded independent central review; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

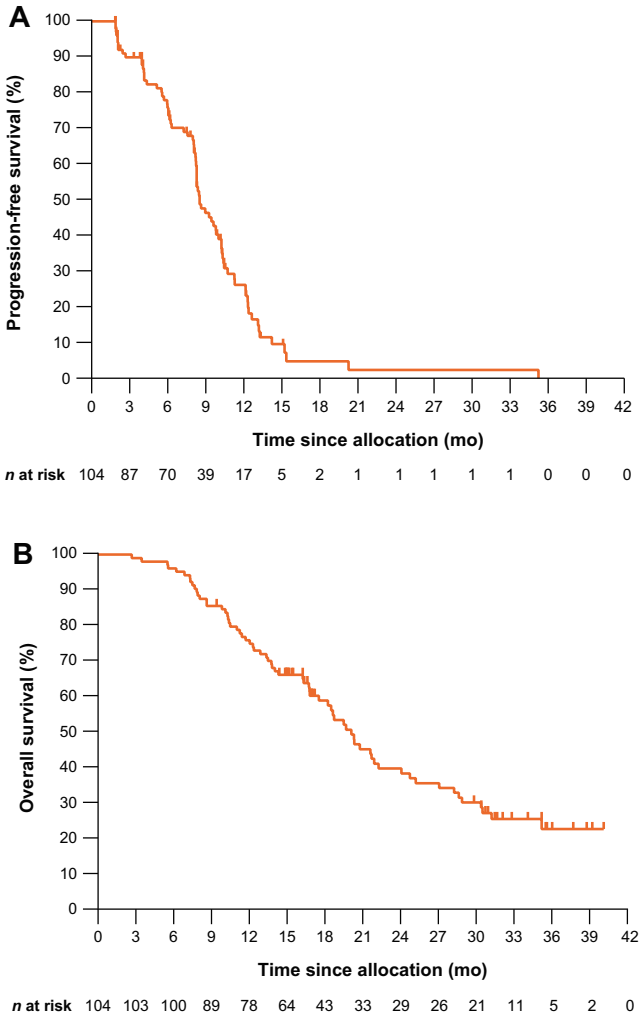

Fig. 3 – Kaplan-Meier estimates of (A) radiographic progression-free survival according to Prostate Cancer Working Group 3–modified Response Evaluation Criteria in Solid Tumors version 1.1 and (B) overall survival.

Grade 3–5 TRAEs occurred in 46 patients (44%). The most frequent TRAEs (incidence ≥20%) were diarrhea, fatigue, alopecia, dysgeusia, nausea, peripheral neuropathy, and asthenia (Table 3). The most frequent grade 3–5 TRAEs (incidence ≥2%) were febrile neutropenia, decreased neutrophil count, anemia, neutropenia, diarrhea, fatigue, pneumonitis, and decreased lymphocyte count. Serious TRAEs occurred in 24 patients (23%; Supplementary Table 3), and 28 (27%) discontinued because of TRAEs (pembrolizumab, *n* = 13 [13%]; docetaxel, *n* = 24 [23%]; prednisone, *n* = 10 [9.6%]).

Sponsor-defined immune-mediated AEs occurred in 34 patients (33%); nine (8.7%) experienced grade 3–5 events (pneumonitis, *n* = 4; colitis, *n* = 4; severe skin reaction, *n* = 1; Supplementary Table 4). The most common immune-mediated AEs (incidence ≥5%) were infusion reactions, hyperthyroidism, pneumonitis, colitis, and hypothyroidism. Of 46 immune-mediated AE episodes, ten (22%) necessitated concurrent systemic corticosteroids with a high starting dose (≥40 mg/d prednisone or equivalent).

Overall, seven patients (6.7%) died of AEs. Five deaths (4.8%) were unrelated to treatment (cerebrovascular accident, *n* = 1; pneumonia, *n* = 2; malignant neoplasm progression, *n* = 2). Two deaths (1.9%) from AEs (both pneumonitis, an immune-mediated AE) were related to treatment as

Table 3 – Treatment-related adverse events with ≥5% incidence among the 104 patients treated with pembrolizumab + docetaxel + prednisone

Treatment-related adverse event	Patients, *n* (%)	
	Any grade	Grade 3–5
Any	100 (96)	46 (44)
Diarrhea	43 (41)	3 (2.9)
Fatigue	43 (41)	3 (2.9)
Alopecia	42 (40)	0 (0)
Dysgeusia	28 (27)	0 (0)
Nausea	27 (26)	0 (0)
Peripheral neuropathy	23 (22)	0 (0)
Asthenia	22 (21)	2 (1.9)
Anemia	19 (18)	5 (4.8)
Decreased appetite	16 (15)	0 (0)
Peripheral edema	15 (14)	1 (1.0)
Mucosal inflammation	13 (13)	0 (0)
Febrile neutropenia	12 (12)	12 (12)
Dyspepsia	11 (11)	0 (0)
Paresthesia	11 (11)	0 (0)
Arthralgia	10 (9.6)	1 (1.0)
Dyspnea	10 (9.6)	0 (0)
Decreased neutrophil count	10 (9.6)	6 (5.8)
Peripheral sensory neuropathy	10 (9.6)	0 (0)
Hyperthyroidism	8 (7.7)	0 (0)
Nail discoloration	8 (7.7)	0 (0)
Nail disorder	8 (7.7)	0 (0)
Neutropenia	8 (7.7)	5 (4.8)
Pruritus	8 (7.7)	0 (0)
Pyrexia	8 (7.7)	0 (0)
Constipation	7 (6.7)	0 (0)
Cough	7 (6.7)	0 (0)
Dry skin	7 (6.7)	0 (0)
Infusion reaction	7 (6.7)	0 (0)
Insomnia	7 (6.7)	0 (0)
Pain in extremity	7 (6.7)	0 (0)
Pneumonitis	7 (6.7)	3 (2.9)
Exertional dyspnea	6 (5.8)	0 (0)
Flushing	6 (5.8)	0 (0)
Decreased lymphocyte count	6 (5.8)	3 (2.9)
Muscle spasms	6 (5.8)	0 (0)
Myalgia	6 (5.8)	0 (0)
Maculopapular rash	6 (5.8)	1 (1.0)

determined by the investigator. One death from pneumonitis occurred 40 d after the patient's last exposure to treatment (4 d after AE onset), and the other occurred 63 d after the patient's last exposure to treatment (13 d after AE onset).

4. Discussion

Combination therapy with pembrolizumab plus docetaxel and prednisone showed a clinical benefit for chemotherapy-naïve patients previously treated with abiraterone or enzalutamide for mCRPC in cohort B of the KEYNOTE-365 study. The confirmed PSA response rate was 34% for patients with baseline PSA measurements, with an ORR of 23% by BICR for those with measurable disease. Antitumor activity was noted in RECIST-measurable and bone-predominant disease, and in PD-L1–positive and PD-L1–negative tumors. The benefit was similar regardless of whether the previous NHA was abiraterone or enzalutamide. Among the patients with RECIST-measurable disease, none experienced CR, and 12 experienced PR as the best response. The target lesion size was reduced in 90% of patients in the current study, with 42% of patients experiencing reductions >30% by BICR. The safety profile of the combination was manageable and consistent with the profiles of the individual agents. The PSA response rate, ORR, and OS observed in the present study are higher than those observed in two cohorts of patients with RECIST-measurable mCRPC in the phase 2 KEYNOTE-199 study of pembrolizumab monotherapy (cohort 1 [PD-L1–positive]: PSA response, 6%; ORR, 6%; OS, 9.5 mo; cohort 2 [PD-L1–negative]: PSA response, 8%; ORR, 3%; OS, 7.9 mo) [18]. However, patients in KEYNOTE-199 previously received docetaxel, whereas patients in KEYNOTE-365 cohort B had chemotherapy-naïve mCRPC.

The efficacy of docetaxel was established in the phase 3 study of docetaxel and prednisone versus mitoxantrone and prednisone in patients with mCRPC who experienced progression during hormone therapy and subsequently received antiandrogen therapy [19]. Docetaxel Q3W led to a 2.4-mo improvement in OS versus mitoxantrone (18.9 vs 16.5 mo; hazard ratio [HR] 0.76, 95% CI 0.62–0.94; p = 0.009). Confirmed PSA levels decreased by ≥50% from baseline in 45% of patients receiving docetaxel and 32% receiving mitoxantrone. In the current study, the confirmed PSA response rate was 34%. The docetaxel versus mitoxantrone study took place before the development of abiraterone and enzalutamide; hence, the data are limited regarding the efficacy of docetaxel after NHA treatment, and the optimal order of therapies is not clear.

The phase 3 FIRSTANA trial compared OS after cabazitaxel (two dose schedules) versus docetaxel in 1168 patients with chemotherapy-naïve mCRPC [20]. For the docetaxel group, the median OS was 24.3 mo, the median time to tumor progression was 12.1 mo, and the tumor response rate (CR or PR) was 31%. However, few patients enrolled in FIRSTANA had previously received enzalutamide or abiraterone. In one retrospective study that included patients from a phase 1/2 abiraterone trial, median OS for patients who received docetaxel after abiraterone was 12.5 mo (95% CI 10.6–19.4), and 13 patients (37%) experienced a PSA decrease of ≥30% [21]. By contrast, the current study showed longer OS after pembrolizumab plus docetaxel and prednisone (20.2 mo, 95% CI 16.9–24.2) than previously reported. Cross-resistance between abiraterone and docetaxel could be the reason why patients receiving docetaxel after abiraterone are more likely to experience disease progression, but additional studies are needed to confirm this hypothesis [21,22]. Enzalutamide has also been used in patients with mCRPC with disease progression after abiraterone. Although the sample size was small (n = 61), a retrospective analysis compared docetaxel (n = 31) and enzalutamide (n = 30) in patients with mCRPC whose disease had progressed on abiraterone [23]. In a multivariable logistic model controlled for baseline and primary refractoriness to previous abiraterone therapy, there was no significant difference between the groups in the odds of a PSA decline of ≥30% (odds ratio 2.17, 95% CI 0.68–7.30; p = 0.20) or ≥50% (odds ratio 1.68, 95% CI 0.51–5.66; p = 0.40). Median PSA PFS was 4.1 mo for both the docetaxel and enzalutamide cohorts (HR 1.35, 95% CI 0.53–3.656); median PFS was 4.7 mo for the enzalutamide cohort and 4.4 mo for the docetaxel cohort (HR, 1.44, 95% CI 0.77–2.71; p = 0.257) [23]. A mouse model of CRPC showed lower

efficacy of docetaxel in mice with enzalutamide-resistant tumors compared with enzalutamide-naïve tumors, similar to the hypothesized cross-resistance between abiraterone and docetaxel [24]. These findings suggest that further study of the optimal sequencing of NHA and chemotherapy agents such as docetaxel may be warranted.

The current study is limited by its small sample size and single-arm design. However, the promising ORR (23%; n = 12 with PR) and OS (20.2 mo) served as a rationale to further investigate this treatment combination in KEYNOTE-921 (NCT03834506). KEYNOTE-921 is a randomized, global, parallel-group, double-blind, phase 3 trial to investigate pembrolizumab (200 mg IV Q3W) plus docetaxel (75 mg/m^2 IV Q3W) and prednisone (5 mg orally twice daily) versus placebo plus docetaxel and prednisone in patients with histologically or cytologically confirmed chemotherapy-naïve mCRPC with disease progression after NHA therapy [25].

The phase 2 CheckMate 9KD study examined the PD-L1 inhibitor nivolumab combined with docetaxel and prednisone. The ORR was 36.8%, with median rPFS of 8.2 mo after minimum follow-up of 28 wk for patients with chemotherapy-naïve mCRPC (65% previously received abiraterone or enzalutamide), similar to the rPFS in the current study (8.5 mo) with comparable safety results [26]. The subsequent phase 3 CheckMate 7DX trial will further investigate this combination.

Mismatch repair deficiency (dMMR), microsatellite instability, and/or hypermutation are believed to be potential enrichment biomarkers for response to immunotherapy in patients with solid tumor malignancies. However, the microsatellite instability-high/dMMR phenotype is rare in mCRPC, affecting only 3–4% of patients [27,28]. There is limited information about and there are no trial data for the response rate to pembrolizumab for this rare prostate cancer population. Therefore, we feel it is unlikely that our findings were significantly affected by these potential enrichment factors.

5. Conclusions

Pembrolizumab plus docetaxel and prednisone demonstrated antitumor activity in chemotherapy-naïve patients with mCRPC previously treated with abiraterone or enzalutamide for mCRPC. OS was longer than observed in previous studies in this population, and the ORR is similarly promising. The safety profile was manageable and consistent with the known profiles of each agent. Our results show activity for this combination, which will be confirmed in the phase 3 KEYNOTE-921 trial.

Author contributions: Evan Y. Yu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Appleman, Berry, Bögemann, Conter, de Bono, Emmenegger, Yu, Gravis, Gurney, Joshua, Kolinsky, Laguerre, Linch, Massard, Mourey, Piulats, Poehlein, Romano, Schloss, Sridhar.
Analysis and interpretation of data: Appleman, Bögemann, Conter, de Bono, Yu, Gurney, Joshua, Kolinsky, Laguerre, Li, Linch, Retz, Massard, Piulats, Poehlein, Romano, Schloss, Sridhar.
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Data sharing statement: Merck Sharp & Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Appendix A. Supplementary data

Peer Review Summary and Supplementary Data associated with this article can be found online at https://doi.org/10.1016/j.eururo.2022.02.023.

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