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Pembrolizumab plus Olaparib in Patients with Metastatic Castration-resistant Prostate Cancer: Long-term Results from the Phase 1b/2 KEYNOTE-365 Cohort A Study

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Abstract

Background: Pembrolizumab and olaparib have shown single-agent activity in patients with previously treated metastatic castration-resistant prostate cancer (mCRPC).
Objective: To evaluate the efficacy and safety of pembrolizumab plus olaparib in mCRPC.
Design, setting, and participants: Cohort A of the phase 1b/2 KEYNOTE-365 study enrolled patients with molecularly unselected, docetaxel-pretreated mCRPC whose disease progressed within 6 mo of screening.
Intervention: Pembrolizumab 200 mg intravenously every 3 wk plus olaparib 400-mg capsule or 300-mg tablet orally twice daily.
Outcome measurements and statistical analysis: The primary endpoints were safety, confirmed prostate-specific antigen (PSA) response rate, and objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by blinded independent central review. The secondary endpoints included radiographic progression-free survival (rPFS) and overall survival (OS).
Results and limitations: Of 104 enrolled patients, 102 were treated. The median age was 70 yr (interquartile range [IQR], 65–76), and 59 patients (58%) had measurable disease as

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per RECIST v1.1. The median time from the first dose to database cutoff was 24 mo (IQR, 22–47). The confirmed PSA response rate was 15%. The confirmed ORR was 8.5% (five partial responses) for patients with measurable disease. The median rPFS was 4.5 mo (95% confidence interval [CI], 4.0–6.5) and median OS was 14 mo (95% CI, 10.4–18.2). Clinical activity was consistent across the programmed death ligand 1 (PD-L1)-positive and homologous recombination repair mutation subgroups. Treatment-related adverse events (TRAEs) occurred in 93 patients (91%). Grade 3–5 TRAEs occurred in 49 patients (48%). Six deaths (5.9%) were due to adverse events; two (myocardial infarction and unknown cause) were attributed to treatment. Limitations of the study include the single-arm design.

Conclusions: Pembrolizumab plus olaparib had a safety profile consistent with the profiles of the individual agents and demonstrated antitumor activity in previously treated patients with molecularly unselected, docetaxel-pretreated mCRPC.

Patient summary: Pembrolizumab plus olaparib showed antitumor activity and expected safety in patients with metastatic castration-resistant prostate cancer.

1. Introduction

Standard-of-care treatment for metastatic prostate cancer is evolving rapidly, with multiple treatment options available for both hormone-sensitive and metastatic castration-resistant prostate cancer (mCRPC) [1,2]. Docetaxel in combination with prednisone was the only life-prolonging treatment for mCRPC until sipuleucel-T, an autologous cellular immunotherapy, was approved in 2010, which demonstrated that immunotherapy can improve outcomes in this disease setting [3–5]. Recent advances in drug development have produced new therapies for mCRPC, including the next-generation hormonal agents (NHAs) abiraterone acetate [6] and enzalutamide [7], poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors [8,9], radium 223 [10], lutetium-177–PSMA-617 [11], and cabazitaxel [12,13]. Despite these advances, mCRPC is incurable, and few treatment options are available to patients whose disease progresses on both docetaxel and NHAs. Therefore, a need exists for novel agents that improve clinical outcomes for patients with mCRPC.

Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, has demonstrated preliminary activity as monotherapy for mCRPC in the open-label phase 1b KEYNOTE-028 and phase 2 KEYNOTE-199 clinical trials [14,15]. Olaparib, a PARP inhibitor, is approved by the US Food and Drug Administration for a subset of patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (*HRR*) gene-mutated mCRPC whose disease has progressed on abiraterone or enzalutamide treatment [16]. In the phase 2 TOPARP-A and TOPARP-B trials, olaparib monotherapy showed activity in patients with mCRPC and aberrations in DNA damage response genes [17,18]. In the phase 3 PROfound study of patients with mCRPC and *BRCA1*, *BRCA2*, or *ATM* gene alterations, olaparib monotherapy demonstrated longer overall (OS) and progression-free (PFS) survival and a higher objective response rate (ORR) than enzalutamide or abiraterone [8,19].

PARP inhibitors can upregulate programmed death ligand 1 (PD-L1) on the tumor cell surface, which could lead to immune activation of the tumor microenvironment and increased sensitivity to PD-1 inhibitors [20]. Even in cells that are homologous recombination proficient, PARP inhibitors amplify STING signaling and promote tumor-infiltrating lymphocytes and antitumor immunity, which can enhance anti–PD-L1 activity in vitro [21]. Therefore, addition of an anti–PD-1/PD-L1 immunotherapy with a PARP inhibitor might enhance antitumor response. Furthermore, pembrolizumab is approved by the US Food and Drug Administration for advanced microsatellite instability–high or mismatch repair–deficient cancer [22]. The phase 1b or 2 KEYNOTE-365 trial (NCT02861573) examined the safety, tolerability, and efficacy of pembrolizumab combination therapies in men with mCRPC, irrespective of *HRR* status. We describe the results from cohort A of KEYNOTE-365, which included patients with molecularly unselected, docetaxel-pretreated mCRPC who were treated with the combination of pembrolizumab and olaparib.

2. Patients and methods

2.1. Study design and patients

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

Male patients aged 18 yr or older with molecularly unselected mCRPC were enrolled. The key eligibility criteria for cohort A were histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology, disease progression within 6 mo before screening (by prostate-specific antigen [PSA] progression as per the Prostate Cancer Working Group 3 [PCWG3] criteria or radiologic bone/soft tissue progression), Eastern Cooperative Oncology Group performance status of 0–2, and previous use of docetaxel for mCRPC.

2.2. Treatment

Patients received pembrolizumab 200 mg intravenously every 3 wk (Q3W) for up to 35 cycles (approximately 24 mo) plus olaparib 400-mg capsules (first 40 patients enrolled) or 300-mg tablets orally twice daily until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. The capsule formulation of olaparib necessitated patients to take a total of 16 capsules per day, whereas the tablet formulation of olaparib is clinically equivalent to the capsule formulation, and provides a reduced pill burden and a more convenient dosing regimen of a total of four tablets per day [23]. If one of the drugs was discontinued because of toxicity, the other drug could be continued at the investigator's discretion.

2.3. Assessments and endpoints

On-study imaging assessments were performed by computed tomography or magnetic resonance imaging and radionuclide bone imaging at baseline and every 9 wk (Q9W) from the date of patient allocation to cohort A through week 54, and every 12 wk (Q12W) thereafter until documented confirmed disease progression, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurred first. PSA was assessed by a central laboratory at screening and Q3W until disease progression. Follow-up time began at the date of patient allocation to cohort A. PD-L1 positivity was defined as a combined positive score (CPS) of $\geq$1 by PD-L1 IHC 22C3 pharmDx (Agilent), in which CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Adverse events (AEs) were monitored throughout the study and for 30 d after the last dose of study drug (90 d for serious AEs). AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Immune-mediated AEs were based on a list of terms specified by the sponsor regardless of attribution to study treatment or immune relatedness by the investigator.

The primary efficacy endpoints were confirmed PSA response (PSA decrease of $\geq$50% from baseline measured twice $\geq$3 wk apart), and ORR (complete response [CR] + partial response [PR]) as per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by blinded independent central review (BICR). Secondary efficacy endpoints were time to PSA progression, ORR as per PCWG3-modified RECIST v1.1 by BICR, duration of response (DOR), disease control rate (DCR; CR or PR + stable disease or non-CR/non–progressive disease [PD] $\geq$6 mo) as per RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR, radiographic PFS (rPFS) as per PCWG3-modified RECIST v1.1 by BICR, and OS. Based on the TOPARP-A study [17], a composite response rate was also a secondary endpoint. The primary safety objective was to characterize the safety and tolerability of pembrolizumab plus olaparib.

Blood for circulating tumor DNA (ctDNA) was collected before the dose on day 1 of cycles 1–3. After cycle 3, ctDNA was collected before the dose Q9W through week 54 and Q12W thereafter, and at treatment discontinuation. Germline status was not specifically tested. Circulating tumor cells were measured using the CELLSEARCH circulating tumor cell test (Veridex LLC, Raritan, NJ, USA). The Guardant360 assay was initially used as it was the only validated ctDNA assay available at that time; the GuardantOMNI assay (Guardant Health, Inc., Redwood City, CA, USA) became available in 2017 and was used for patients subsequently enrolled in cohort A. *BRCA1*, *BRCA2*, and *ATM* mutations were detected using Guardant360. Formalin-fixed, paraffin-embedded tissue was analyzed by FoundationOne CDx assay (Foundation Medicine, Inc., Cambridge, MA, USA). Most tissues were archival and biopsied within 1 yr of screening and after diagnosis of mCRPC, although some patients provided older archival tissue. *BRCA1*, *BRCA2*, and *ATM* mutations were detected using Guardant360 (Guardant Health, Inc.). The *HRR* genes evaluated for mutational status using GuardantOMNI (Guardant Health, Inc.) or FoundationOne CDx (Foundation Medicine, Inc.) were *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. Both Guardant360 and GuardantOMNI have a 96–100% positive predictive value for single nucleotide variants, copy number variations, fusions, and indels [24,25]. Based on American College of Medical Genetics guidelines, only known pathogenic mutations were classified as mutations, and variants of uncertain significance were not classified as mutations [26]. Mutational status classified as unknown included cases in which there were no available samples (tissue or plasma), there was insufficient DNA, or assay results did not meet quality control. The Guardant360 test is a 73-gene panel validated for the detection of single nucleotide variations, insertion and deletion alterations, copy number alterations (CNAs), and fusions in all guideline-recommended indications for advanced solid tumors [27]. The GuardantOMNI comprehensive genomic profiling tool is a 500-gene panel that incorporates the majority of genes being evaluated in cancer drug development pipelines and biomarkers for immuno-oncology applications, including tumor mutational burden. FoundationOne CDx is a next-generation sequencing-based in vitro diagnostic device for the detection of substitutions, indels, and CNAs in 309 cancer-related genes, one promoter region, one noncoding RNA, and select intronic regions from 36 commonly rearranged genes [28].

2.4. Statistical considerations

Efficacy and safety were assessed in all patients who received at least one dose of study treatment. For ORR, patients must have had measurable disease as per RECIST v1.1 at baseline. DOR was evaluated only for patients with an objective response. The point estimates and 95% confidence intervals (CIs) for PSA response rate, ORR, DCR, and composite response rate were evaluated using the Clopper-Pearson method. The Kaplan-Meier method was used to estimate DOR, time to PSA progression, rPFS, and OS.

3. Results

3.1. Disposition, demographics, and exposure

Between January 17, 2017, and December 2, 2019, 165 patients were screened for enrollment into cohort A. Of these 165 patients, 61 were excluded and 104 were enrolled (Supplementary Fig. 1). Two patients were not treated because of a screening failure (n = 1) and physician decision (n = 1). The median age was 70 yr (interquartile range [IQR], 65–76), 29 patients (28%) had PD-L1–positive tumors, and 59 patients (58%) had measurable disease per RECIST v1.1 (Table 1). All patients received prior docetaxel, and 40 patients (39%) received prior cabazitaxel. Most patients (92%) received prior abiraterone and/or enzalutamide treatment; 45% of patients received both abiraterone and enzalutamide. The median time from allocation to data cutoff was 24 mo (IQR, 22–47). As of March 29, 2021, 95 patients (93%) had discontinued treatment, primarily because of clinical or radiographic PD (72%; Supplementary Fig. 1). Patients received a median of 7.5 administrations (IQR, 4–14) of pembrolizumab and a median olaparib daily dose of 600 mg (IQR, 590–778). The median duration of therapy was 4.9 mo (IQR, 2.6–9.7) for pembrolizumab and 5.4 mo (IQR, 2.8–10.1) for olaparib.

Table 1 – Patient demographics and baseline characteristics

Characteristic	Pembrolizumab + olaparib (*N* = 102)
Age (yr), median (IQR)	70 (65–76)
≥65 yr, *n* (%)	79 (77)
Race, *n* (%)	
White	84 (82)
Black or African American	3 (2.9)
American Indian or Alaska native	1 (1.0)
Asian	1 (1.0)
Multiple	1 (1.0)
Native Hawaiian or other Pacific Islander	1 (1.0)
Missing	11 (11)
Geographic region of enrolling site, *n* (%)	
North America	27 (26)
Western Europe	62 (61)
Rest of the world	13 (13)
ECOG PS, *n* (%)	
0	48 (47)
1	48 (47)
2	6 (5.9)
Baseline ALP value (IU/l), median (range)	101 (23–865)
Baseline HgB value (g/dl), median (range)	12 (9.6–15)
Baseline LDH value (IU/l), median (range)	222 (120–1857)
PSA value (ng/ml), median (IQR)	109 (30–480)
PD-L1 status, *n*(%)	
Positive[a]	29 (28)
Negative	28 (27)
Unknown	45 (44)[b]
Disease measurable as per RECIST v1.1, *n* (%)	59 (58)
Baseline tumor size (mm)[c], median (IQR)	75 (41–124)
Visceral disease[d], *n* (%)	34 (33)
Metastatic staging[e], *n* (%)	
M1	66 (65)
M1A	2 (2.0)
M1B	24 (23)
M1C	10 (9.8)
History of brain metastases, *n* (%)	0 (0.0)
Prior use of docetaxel, *n* (%)	102 (100)
Prior use of cabazitaxel, *n* (%)	40 (39)
Prior use of abiraterone/enzalutamide, *n* (%)	
Abiraterone only	24 (24)
Enzalutamide only	24 (24)
Abiraterone and enzalutamide	46 (45)
Neither	8 (7.8)

ALP = alkaline phosphatase; BICR = blinded independent central review; CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group performance status; HgB = hemoglobin; IQR = interquartile range; LDH = lactate dehydrogenase; PD-L1 = programmed death ligand 1; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] PD-L1 positive was defined as CPS ≥1. CPS was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

[b] Thirty-two patients had bone-only disease.

[c] Assessed by BICR as per RECIST v1.1.

[d] Soft tissue (not in brain, bone, or lymph nodes).

[e] Patients with M1 designation may not have been subdivided into A, B, or C categories.

3.2. Genomic analysis

The Guardant360 assay was used for the first 42 patients enrolled in the study, and the GuardantOMNI assay was used for 60 subsequently enrolled patients. By a ctDNA analysis, three patients had a *BRCA* gene mutation (*n* = 2 *BRCA2*; *n* = 1 *BRCA1*) and 14 had an *HRR* gene mutation. Notably, no *HRR* mutations were detected using the Guardant360 assay (first 42 patients), and plasma-negative results were classified as unknown because mutational status was uncertain. Of 76 patient samples with soft tissue available for FoundationOne CDx analysis, 41 passed quality control successfully. Twelve patients had *HRR* mutations, four had a *BRCA* mutation, and no microsatellite instability alterations were detected. The overall percentage agreement between Guardant Health and FoundationOne CDx assays was 98% for *BRCA* mutation status and 87% for *HRR* status (Supplementary Table 1). In at least one assay, 18 of 102 patients (18%) had tumors identified as having an *HRR* mutation, and four (3.9%) had a *BRCA* mutation.

3.3. Efficacy

The confirmed PSA response rates in patients with a baseline PSA measurement were 15% (15/102) for the total population and 19% (11/59) for patients with RECIST-measurable disease. Overall, of 102 patients, 51 (50%) had any reduction in PSA from baseline (confirmed and unconfirmed) and 19 (19%) had ≥50% PSA reduction from baseline (confirmed and unconfirmed; Fig. 1A). The median time to confirmed PSA progression was 4.0 mo (95% CI, 3.0–4.9; Fig. 1B). PSA response rates were generally consistent across subgroups, including in the PD-L1 and *HRR* mutation subgroups, although the analysis is limited by a low patient population in certain subgroups (Supplementary Fig. 2A and Supplementary Table 2).

By BICR as per RECIST v1.1, ORR was 8.5% (five PRs) in patients with RECIST-measurable disease (Table 2). For all 102 treated patients, the DCR was 26%. Similar to PSA response rate, ORR and DCR were generally consistent between subgroups, including the PD-L1 and *HRR* mutation subgroups (Supplementary Fig. 2B and 2C, and Supplementary Table 2). Thirty-four patients (58%) with RECIST-measurable disease experienced a reduction in target lesion size from baseline (confirmed and unconfirmed); 11 (19%) experienced a >30% reduction (Fig. 2A). The median time to response was 8.3 mo (IQR, 2.1–8.8; Fig. 2B). The median DOR was 24 mo (IQR, 8.3–12.3), and 75% of responses were ongoing at 12 mo by the Kaplan-Meier estimate. The composite response rate (confirmed objective response, confirmed PSA response, or a circulating tumor cell response reduction of circulating tumor cells from five or more cells per 7.5 ml blood at baseline to fewer than five cells per 7.5 ml blood during treatment) was 18% in the total population, 24% in patients with RECIST-measurable disease, and 9.3% in patients without measurable disease.

By BICR as per PCWG3-modified RECIST v1.1, ORR was 12% (seven PRs) in patients with measurable disease. DCR was 36% in all treated patients (Supplementary Table 3). The median time to response was 8.3 mo (IQR, 2.1–8.8), and the median DOR was not reached; 83% of responses were ongoing at 12 mo by the Kaplan-Meier estimate.

In all 102 treated patients, the median rPFS was 4.5 mo (95% CI, 4.0–6.5), the 6-mo rPFS rate was 47%, and the 12-mo rPFS rate was 27% (Fig. 3A). The median OS was 14 mo (95% CI, 10.4–18.2; Fig. 3B). The 6-mo OS rate was 80%, and the 12-mo OS rate was 56%. The median rPFS was 4.1mo (95% CI, 2.1–13) in the PD-L1–positive subgroup and 5.2 mo (95% CI, 4.0–11) in the PD-L1–negative subgroup (Supplementary Fig. 3A). The median OS was 10 mo (95% CI,

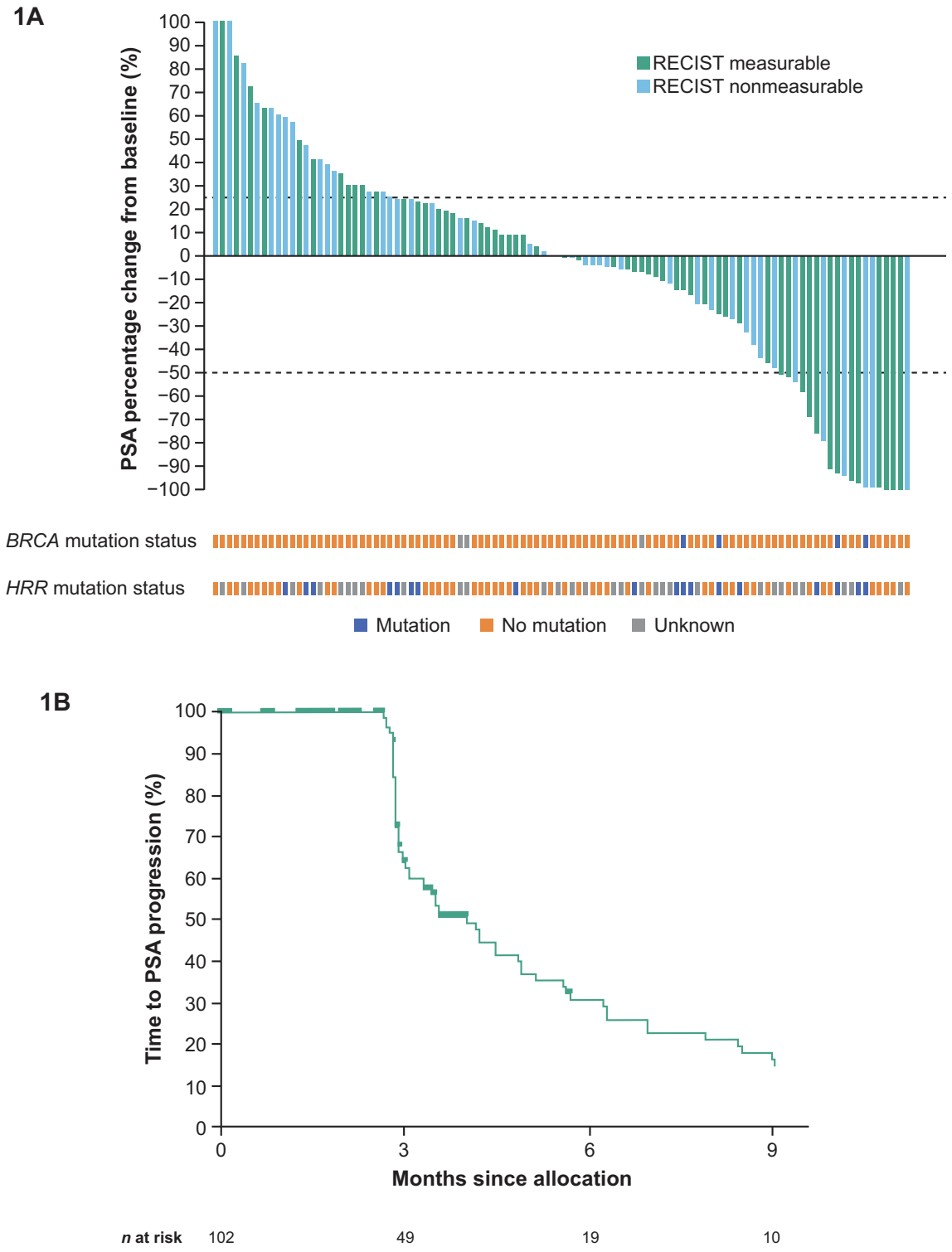

Fig. 1 – (A) PSA percentage change from baseline (confirmed and unconfirmed) and (B) Kaplan-Meier estimate of time to PSA progression. CI = confidence interval; HRR = homologous recombination repair; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

6.5–20) in the PD-L1–positive subgroup and 18 mo (95% CI, 7.7–31) in the PD-L1–negative subgroup (Supplementary Fig. 3B). By *HRR* status, the median rPFS was 6.5 mo (95% CI, 2.1–14.1) and the median OS was 8.9 mo (95% CI, 6.5–18) in patients with an *HRR* mutation (Supplementary Fig. 4A and 4B). In patients with no *HRR* mutation, the median rPFS was 4.5 mo (95% CI, 4.0–11) and the median OS was 17 mo (95% CI, 10–31; Supplementary Fig. 4A and 4B).

Table 2 – Confirmed best response by BICR assessment as per RECIST v1.1

Characteristic	RECIST-measurable disease (n = 59)	RECIST-nonmeasurable disease (n = 43)	Total (N = 102)
ORR, % (95% CI)	8.5 (2.8–19)	NA	NA
DCR[a], % (95% CI)	25 (15–38)	28 (15–44)	26 (18–36)
Best response, n (%)			
CR	0 (0.0)	NA	0 (0.0)
PR	5 (8.5)	NA	5 (4.9)
SD of any duration	20 (34)	0 (0.0)	20 (20)
Non-CR/non-PD	0 (0.0)	23 (53)	23 (23)
SD or non-CR/non-PD ≥6 mo	10 (17)	12 (28)	22 (22)
PD	30 (51)	17 (40)	47 (46)
Nonevaluable	0 (0.0)	2 (4.7)	2 (2.0)
No assessment	4 (6.8)	1 (2.3)	5 (4.9)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; NA = not applicable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Defined as the proportion of patients who had an objective response (CR or PR) or who had SD or non-CR/non-PD for at least 6 mo.

3.4. Safety

All 102 treated patients (100%) experienced at least one all-cause AE, and grade 3–5 AEs occurred in 74 patients (73%; Supplementary Table 4). Treatment-related AEs occurred in 93 patients (91%; Table 3). Grade 1 treatment-related AEs occurred in 17 patients (17%), grade 2 treatment-related AEs occurred in 27 patients (26%), and grade 3–5 treatment-related AEs occurred in 49 patients (48%). Nineteen patients (19%) discontinued treatment because of treatment-related AEs. Olaparib-related AEs occurred in 89 patients (87%); 45 patients (44%) experienced grade 3–5 olaparib-related AEs (Table 3). Pembrolizumab-related AEs occurred in 75 patients (74%); 20 patients (20%) experienced grade 3–5 pembrolizumab-related AEs (Table 3). Twenty patients (20%) had a serious treatment-related AE (Supplementary Table 4).

Immune-mediated AEs occurred in 12 patients (12%), with four (3.9%) experiencing events with a toxicity grade 3–5 (pneumonitis [n = 2], adrenal insufficiency [n = 1], and severe skin reaction [n = 1]; Supplementary Table 5). Six patients (5.8%) received corticosteroids to manage immune-mediated AEs. Three of 15 episodes (20%) of immune-mediated AEs were treated with high-dose corticosteroids (≥40 mg/d prednisone or equivalent).

Overall, six patients (5.9%) died of AEs. Four deaths (3.9%) occurred from AEs considered unrelated to treatment by the investigator (colorectal cancer [n = 1], general health deterioration [n = 1], *Pneumocystis jirovecii* pneumonia [n = 1], and unknown cause [n = 1]); two deaths (1.9%) from AEs were determined by the investigator to be treatment related (myocardial infarction [n = 1] and unknown cause [n = 1]).

4. Discussion

Advances in therapy over the past decade have improved survival and quality of life for patients with mCRPC. However, the median OS for patients with metastatic disease treated with newer therapies is approximately 2.8 yr, indicating a need for novel agents that may improve patient outcomes [29]. In the present study, pembrolizumab plus olaparib demonstrated durable antitumor activity in a limited number of men with molecularly unselected docetaxel-pretreated mCRPC in cohort A of the KEYNOTE-365 study. The confirmed PSA response rate was 15%, with an ORR of 8.5% and a DCR of 26% by BICR as per RECIST v1.1. The ORR was generally consistent across subgroups in this study.

This was a heavily pretreated population; 92% of patients had previously received both docetaxel and enzalutamide and/or abiraterone treatment, 39% had previously received cabazitaxel, and 45% had previously received both abiraterone and enzalutamide. Interim results from the COSMIC-021 study of cabozantinib in combination with atezolizumab showed an ORR of 15% in patients with mCRPC who had previously received enzalutamide and/or abiraterone treatment; however, only 25% of patients had previously received docetaxel for metastatic hormone-sensitive prostate cancer [30]. Other studies have reported limited success in this heavily pretreated patient population. In the phase 3 COMET-1 study, cabozantinib did not improve OS compared with prednisone (11 vs 9.8 mo, p = 0.213) in patients with progressive mCRPC who had previously received docetaxel [31]. A lack of success has also been reported in a heavily pretreated mCRPC population that received radium-223 [32]. An increase in PSA level was observed in 20 of 29 patients (69%) in a retrospective study of patients with mCRPC treated with radium-223; 52% (15/29) of patients had a >50% increase in PSA [32]. Satraplatin, a fourth-generation oral platinum compound, plus prednisone was compared with placebo plus prednisone for chemotherapy-refractory mCRPC [33]. Compared with placebo (n = 315), satraplatin plus prednisone (n = 635) was associated with a benefit in PFS (median, 11 vs 9.7 wk; hazard ratio [HR], 0.67; 95% CI, 0.57–0.77; p < 0.001) but not in OS (median, 61 vs 61 wk; HR, 0.98; 95% CI, 0.84–1.2; p = 0.80).

Patients in this study were not preselected by biomarker status. In a biomarker-defined subgroup of patients with mCRPC who had DNA-repair defects in the phase 2 TOPARP-A trial, a composite response rate of 88% was observed with olaparib monotherapy [17]. These results were confirmed in the phase 2 TOPARP-B trial of patients with mCRPC and aberrations in DNA damage response genes, including *BRCA1/2*, *ATM*, *CDK12*, and *PALB2*; the greatest antitumor activity was observed in patients with *BRCA1/2* mutations (ORR, 52%) [18]. Patients with mCRPC enrolled in the phase 3 PROfound study whose tumors were *HRR* mutation positive had longer median OS when treated with olaparib than patients treated with an NHA (19 vs 15mo) [8].

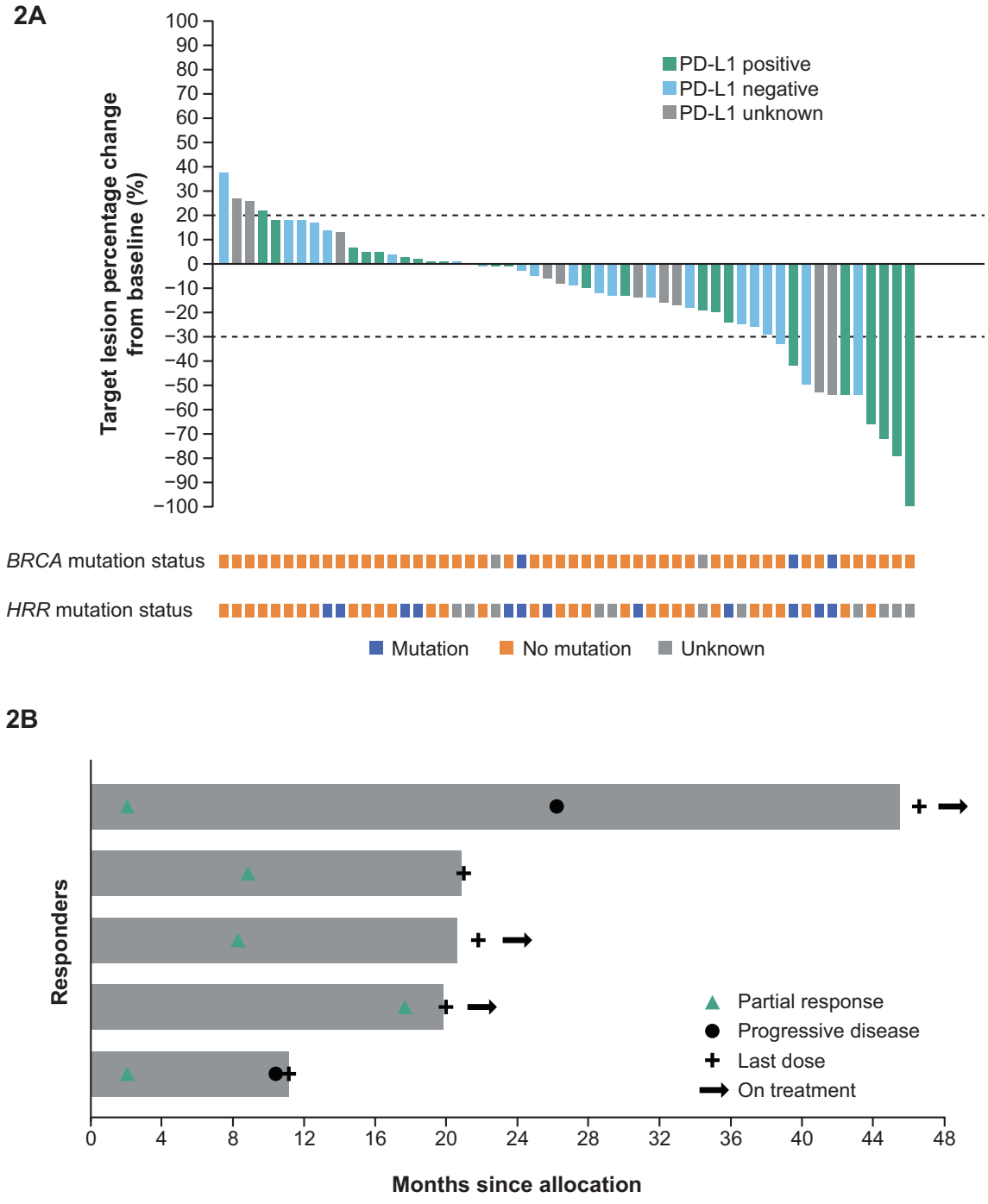

Fig. 2 – (A) Best target lesion percentage change from baseline (confirmed and unconfirmed) and (B) time to response by BICR as per RECIST v1.1. BICR = blinded independent central review; HRR = homologous recombination repair; NE = nonevaluable; NR = not reached; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Previous studies have also shown antitumor activity of pembrolizumab monotherapy in prostate cancer. In the phase 1b KEYNOTE-028 study, pembrolizumab monotherapy demonstrated antitumor activity in heavily pretreated patients with mCRPC with PD-L1–positive prostate cancer with an ORR of 17% and a median DOR of 14 mo [14]. Pembrolizumab monotherapy also demonstrated antitumor activity and disease control in the phase 2 KEYNOTE-199 study; an ORR of 3.9%, a DCR of 26%, and median OS of 9.6mo were observed among all patients with either RECIST-measurable or bone-predominant mCRPC who previously received docetaxel and NHA therapy (eg, enzalutamide or abiraterone) [14,15]. In patients with solid tumors with mismatch repair gene mutations, an ORR of 53%, which included 18 CRs, was observed with pembrolizumab monotherapy; these results led to a regulatory

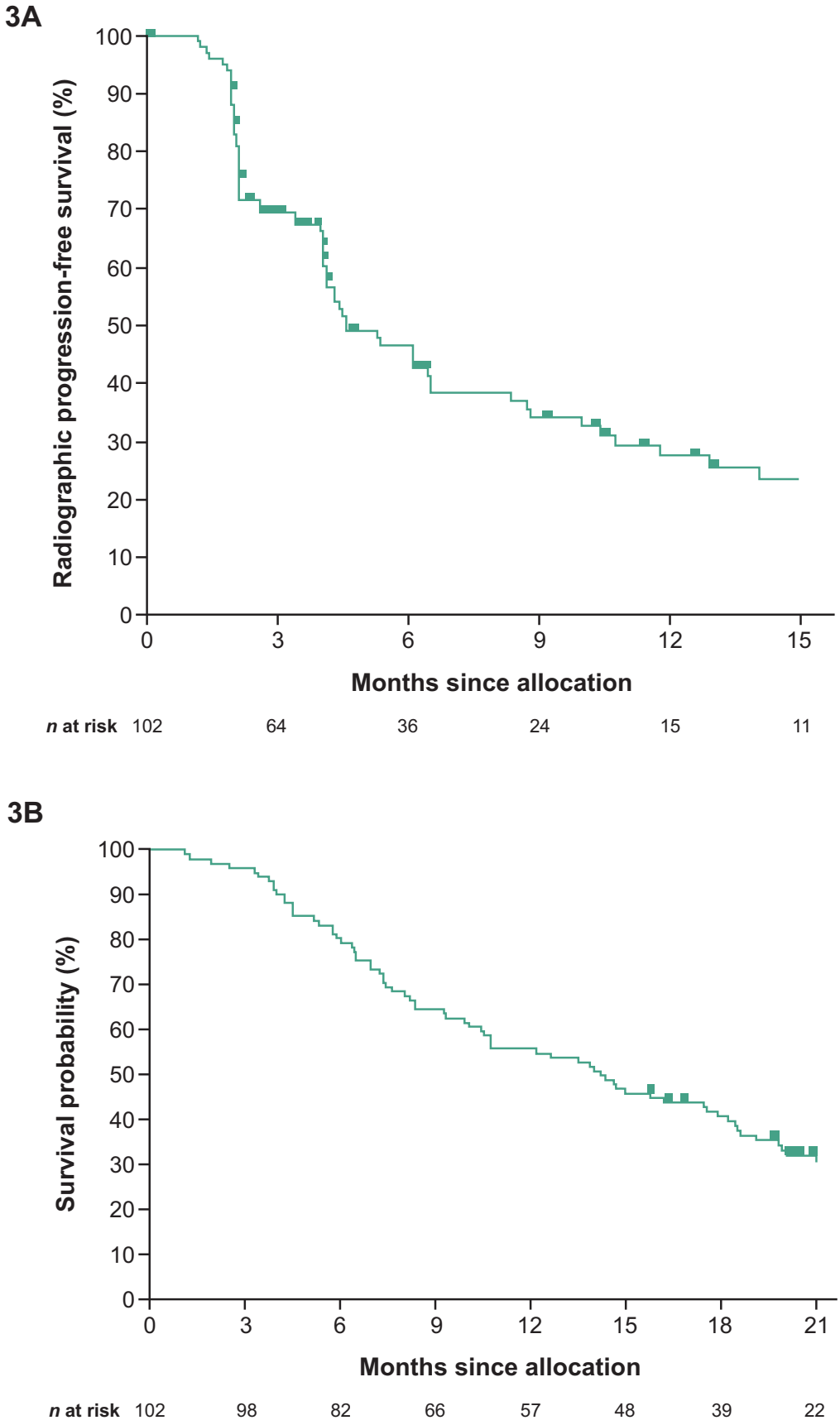

Fig. 3 – Kaplan-Meier estimates of (A) radiographic progression-free survival as per PCWG3-modified RECIST v1.1 and (B) overall survival. CI = confidence interval; PCWG3 = Prostate Cancer Working Group 3; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 3 – Pembrolizumab- and/or olaparib-related adverse events with ≥3% incidence

Treatment-related adverse event, *n* (%)	Pembrolizumab + olaparib (*N* = 102)		Olaparib-related (*N* = 102)		Pembrolizumab-related (*N* = 102)	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Any	93 (91)	49 (48)	89 (87)	45 (44)	75 (74)	20 (20)
Anemia	42 (41)	28 (27)	42 (41)	28 (27)	6 (5.9)	3 (2.9)
Nausea	42 (41)	2 (2.0)	41 (40)	2 (2.0)	15 (15)	1 (1.0)
Decreased appetite	31 (30)	0 (0.0)	31 (30)	0 (0.0)	15 (15)	0 (0.0)
Fatigue	31 (30)	6 (5.9)	29 (28)	6 (5.9)	22 (22)	3 (2.9)
Asthenia	29 (28)	4 (3.9)	28 (27)	4 (3.9)	24 (24)	2 (2.0)
Vomiting	27 (26)	1 (1.0)	27 (26)	1 (1.0)	11 (11)	0 (0.0)
Diarrhea	23 (23)	0 (0.0)	18 (18)	0 (0.0)	17 (17)	0 (0.0)
Neutropenia	12 (12)	5 (4.9)	12 (12)	5 (4.9)	1 (1.0)	0 (0.0)
Pruritus	11 (11)	0 (0.0)	4 (3.9)	0 (0.0)	11 (10.8)	0 (0.0)
Rash	10 (9.8)	1 (1.0)	4 (3.9)	1 (1.0)	9 (8.8)	1 (1.0)
Blood creatinine increased	9 (8.8)	0 (0.0)	7 (6.9)	0 (0.0)	4 (3.9)	0 (0.0)
Weight decreased	9 (8.8)	0 (0.0)	9 (8.8)	0 (0.0)	3 (2.9)	0 (0.0)
Thrombocytopenia	7 (6.9)	2 (2.0)	7 (6.9)	2 (2.0)	1 (1.0)	0 (0.0)
Arthralgia	5 (4.9)	0 (0.0)	4 (3.9)	0 (0.0)	3 (2.9)	0 (0.0)
Dysgeusia	5 (4.9)	0 (0.0)	5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.9)	0 (0.0)
Constipation	4 (3.9)	0 (0.0)	4 (3.9)	0 (0.0)	3 (2.9)	0 (0.0)
Cough	4 (3.9)	0 (0.0)	3 (2.9)	0 (0.0)	3 (2.9)	0 (0.0)
Dizziness	4 (3.9)	0 (0.0)	4 (3.9)	0 (0.0)	2 (2.0)	0 (0.0)
Dyspnea	4 (3.9)	1 (1.0)	3 (2.9)	1 (1.0)	3 (2.9)	1 (1.0)
Platelet count decreased	4 (3.9)	1 (1.0)	4 (3.9)	1 (1.0)	1 (1.0)	0 (0.0)

approval through the US Food and Drug Administration in patients with microsatellite instability–high or mismatch repair–deficient cancer [22,34]. Although olaparib monotherapy is approved for patients with an *HRR* gene mutation [16], the combination of pembrolizumab and olaparib demonstrates activity regardless of *HRR* mutation status. Notably, olaparib plus abiraterone has shown significant improvement in rPFS compared with abiraterone alone in patients with mCRPC regardless of mutational status [35].

Pembrolizumab plus olaparib had an expected safety profile, which was consistent with the profiles of the individual agents [8,36]. The most common treatment-related AEs of any grade were anemia (41%) and nausea (41%). A greater percentage of patients had grade 3–5 AEs related to olaparib (44%) than related to pembrolizumab (20%).

The current study is limited by its open-label design and lack of comparator group. Although clinical outcomes were largely consistent across subgroups, PD-L1 status was unknown in 44% of patients, and results should be interpreted with caution. There were also a limited number of patients with an *HRR* mutation, determined from the heterogeneity of testing assays. The observed activity in this study, independent of PD-L1 or *HRR* mutation status, served as a rationale to further investigate this treatment combination in the ongoing phase 3 KEYLYNK-010 trial (NCT03834519). KEYLYNK-010 was a randomized, global, parallel-group, open-label phase 3 trial investigating the combination of pembrolizumab plus olaparib versus abiraterone or enzalutamide in abiraterone- or enzalutamide-pretreated patients with docetaxel-pretreated mCRPC. Although the median OS of 14 mo observed in this analysis was considered comparable with the existing literature in patients previously treated with docetaxel, no survival benefit was observed between pembrolizumab plus olaparib versus abiraterone acetate or enzalutamide in the KEYLYNK-010 trial [31,33,37–40].

5. Conclusions

The combination of pembrolizumab plus olaparib demonstrated limited antitumor activity and had an expected safety profile in patients with molecularly unselected docetaxel-pretreated mCRPC. Biomarker data suggest that antitumor activity with this treatment combination is independent of PD-L1 or *HRR* mutation status.

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References

[1] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Prostate cancer. Version 4.2019. National Comprehensive Cancer Network; 2019.

[2] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.

[3] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.

[4] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

[5] Corporation D. PROVENGE® (sipuleucel-T) suspension for intravenous infusion. Seattle, WA: Dendreon Corporation; 2014.

[6] Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.

[7] Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol 2017;71:151–4.

[8] Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020;383:2345–57.

[9] Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study. Clin Cancer Res 2020;26:2487–96.

[10] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.

[11] Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021;385:1091–103.

[12] Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m^2) and the currently approved dose (25 mg/m^2) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. J Clin Oncol 2017;35:3198–206.

[13] de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019;381:2506–18.

[14] Hansen AR, Massard C, Ott PA, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann Oncol 2018;29:1807–13.

[15] Goh JC, Puilats Rodriguez JM, Gross-Goupil M, et al. Phase II study of pembrolizumab in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer (mCRPC): updated follow-up of cohorts (C) one to three from KEYNOTE-199. J Clin Oncol 2020;38:e17584.

[16] AstraZeneca Pharmaceuticals LP. LYNPARZA^R (olaparib) tablets, for oral use. December 2020. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020

[17] Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697–708.

[18] Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:162–74.

[19] de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091–102.

[20] Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017;23:3711–20.

[21] Shen J, Zhao W, Ju Z, et al. PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. Cancer Res 2019;79:311–9.

[22] Merck & Co., Inc. KEYTRUDA® (pembrolizumab) injection, for intravenous use. March 2022. Whitehouse Station, NJ: Merck & Co., Inc.; 2022.

[23] Mateo J, Moreno V, Gupta A, et al. An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. Target Oncol 2016;11:401–15.

[24] Helman E, Artieri C, Vowles JV, et al. Abstract 5603: Analytical validation of a comprehensive 500-gene ctDNA panel designed for immuno-oncology and DNA damage research. Cancer Res 2018;78:5603.

[25] Vowles J, Odegaard J, Mortimer S, et al. Abstract 5705: Analytical validation of Guardant360 v2.10. Cancer Res 2017;77:5705.

[26] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–24.

[27] Odegaard JI, Vincent JJ, Mortimer S, et al. Validation of a plasma-based comprehensive cancer genotyping assay utilizing orthogonal tissue- and plasma-based methodologies. Clin Cancer Res 2018;24:3539–49.

[28] Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31:1023–31.

[29] Francini E, Gray KP, Shaw GK, et al. Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry. Prostate Cancer Prostatic Dis 2019;22:420–7.

[30] Agarwal N, McGregor BA, Maughan BL, et al. LBA24 Cabozantinib (C) in combination with atezolizumab (A) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): results of expanded cohort 6 of the COSMIC-021 study. Ann Oncol 2021;32(suppl_5):S1283–346.

[31] Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. J Clin Oncol 2016;34:3005–13.

[32] Modi D, Hwang C, Mamdani H, et al. Radium-223 in heavily pretreated metastatic castrate-resistant prostate cancer. Clin Genitourin Cancer 2016;14:373–380.e2.

[33] Sternberg CN, Petrylak DP, Sartor O, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: the SPARC trial. J Clin Oncol 2009;27:5431–8.

[34] Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409–13.

[35] Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant

prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018;19:975–86.
[36] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395–405.
[37] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[38] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[39] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[40] Merck & Co. Merck announces KEYLYNK-010 trial evaluating KEYTRUDA® (pembrolizumab) in combination with LYNPARZA® (olaparib) in patients with metastatic castration-resistant prostate cancer to stop for futility. 2022. https://www.merck.com/news/merck-announces-keylynk-010-trial-evaluating-keytruda-pembrolizumab-in-combination-with-lynparza-olaparib-in-patients-with-metastatic-castration-resistant-prostate-cancer-to-stop-for-f/.