Pembrolizumab Plus Olaparib for Patients With Previously Treated and Biomarker-Unselected Metastatic Castration-Resistant Prostate Cancer: The Randomized, Open-Label, Phase III KEYLYNK-010 Trial

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ABSTRACT

PURPOSE There is an unmet need for therapeutic options that prolong survival for patients with heavily pretreated, metastatic castration-resistant prostate cancer (mCRPC). The phase III, open-label KEYLYNK-010 study evaluated pembrolizumab plus olaparib versus a next-generation hormonal agent (NHA) for biomarker-unselected, previously treated mCRPC.

METHODS Eligible participants had mCRPC that progressed on or after abiraterone or enzalutamide (but not both) and docetaxel. Participants were randomly assigned (2:1) to pembrolizumab plus olaparib or NHA (abiraterone or enzalutamide). The dual primary end points were radiographic progression-free survival (rPFS) by blinded independent central review per Prostate Cancer Working Group–modified RECIST 1.1 and overall survival (OS). Time to first subsequent therapy (TFST) was a key secondary end point. Safety and objective response rate (ORR) were secondary end points.

RESULTS Between May 30, 2019, and July 16, 2021, 529 participants were randomly assigned to pembrolizumab plus olaparib and 264 to NHA. At final rPFS analysis, median rPFS was 4.4 months (95% CI, 4.2 to 6.0) with pembrolizumab plus olaparib and 4.2 months (95% CI, 4.0 to 6.1) with NHA (hazard ratio [HR], 1.02 [95% CI, 0.82 to 1.25]; $P = .55$). At final OS analysis, median OS was 15.8 months (95% CI, 14.6 to 17.0) and 14.6 months (95% CI, 12.6 to 17.3), respectively (HR, 0.94 [95% CI, 0.77 to 1.14]; $P = .26$). At final TFST analysis, median TFST was 7.2 months (95% CI, 6.7 to 8.1) versus 5.7 months (95% CI, 5.0 to 7.1), respectively (HR, 0.86 [95% CI, 0.71 to 1.03]). ORR was higher with pembrolizumab plus olaparib versus NHA (16.8% *v* 5.9%). Grade ≥3 treatment-related adverse events occurred in 34.6% and 9.0% of participants, respectively.

CONCLUSION Pembrolizumab plus olaparib did not significantly improve rPFS or OS versus NHA in participants with biomarker-unselected, heavily pretreated mCRPC. The study was stopped for futility. No new safety signals occurred.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Next-generation hormonal agents (NHAs) and docetaxel are mainstays of first-line metastatic castration-resistant prostate cancer (mCRPC) setting and in combination with androgen deprivation therapy (ADT) in the metastatic hormone-sensitive prostate cancer (mHSPC) setting.[1,2] Therapeutic approaches for biomarker-unselected mCRPC after NHA and docetaxel include NHA switch, cabazitaxel, and recently the radioligand lutetium-177-PSMA-617

CONTEXT

Key Objective

Does the combination of pembrolizumab plus olaparib yield better outcomes than a next-generation hormonal agent (NHA) switch for patients with metastatic castration-resistant prostate cancer after receipt of one prior NHA and docetaxel?

Knowledge Generated

Pembrolizumab plus olaparib did not significantly improve radiographic progression-free survival or overall survival versus NHA switch in the randomized, double-blind, phase III KEYLYNK-010 study. Pembrolizumab plus olaparib was associated with more adverse events compared with NHA treatment, but the safety profile of this combination did not suggest additive toxicity.

Relevance *(M.A. Carducci)*

This internationally conducted study is one a recent string of studies reinforcing the challenges associated with the immunosuppressive tumor microenvironment found in prostate cancer. Although discouraging, continued exploration of immune checkpoint inhibitors with other novel agents based on preclinical and clinical studies such as this is needed.*

*Relevance section written by *JCO* Associate Editor Michael A. Carducci, MD, FACP, FASCO.

(^{177}Lu-prostate-specific membrane antigen [PSMA]-617),[1-5] but additional active regimens supported by high levels of evidence are needed.

Immune checkpoint inhibitors demonstrated antitumor activity in certain patients with prostate cancer, although none are recommended by guidelines for biomarker-unselected mCRPC.[1,2] The anti-PD-1 antibody pembrolizumab may be used for a subset of patients on the basis of its approvals for the treatment of unresectable or metastatic microsatellite instability-high (MSI-high), mismatch repair deficient, or tumor mutational burden-high (TMB ≥10 mutations/megabase) solid tumors, as determined by a Food and Drug Administration–approved test, that progressed after prior treatment and have no satisfactory alternative options in the United States.

Preclinical models and human studies suggest that prostate cancer has an immunosuppressive tumor microenvironment (TME) with low effector T-cell infiltration.[6-8] Aggressive, heavily pretreated, and advanced prostate cancers are associated with increased PD-L1 expression,[9-11] and may be susceptible to immunotherapy plus combination partners targeting immunosuppression.[12] The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib is approved for the treatment of patients with mCRPC with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutations (in the United States) or *BRCA1* or *BRCA2* mutations (in the European Union and Japan) that progressed after NHA treatment. The phase III PROpel study reported that the addition of olaparib to first-line abiraterone for mCRPC with or without HRR mutations significantly improved imaging-based progression-free survival (PFS; hazard ratio [HR], 0.66 [95% CI, 0.54 to 0.81]; $P < .001$); median overall survival (OS) was prolonged by >7 months (maturity, 47.9%; HR, 0.81 [95% CI, 0.67 to 1.00]; $P = .054$).[13,14] Preclinical evidence suggests PARP inhibitors may sensitize tumors to immune checkpoint inhibitor therapy by upregulating tumor cell PD-L1 expression and activating STING-dependent pathways independent of BRCA mutational status.[15,16] Pembrolizumab plus olaparib showed antitumor activity and a safety profile consistent with the individual agents in participants with biomarker-unselected, docetaxel-pretreated mCRPC in Cohort A of the phase Ib/II KEYNOTE-365 study.[17,18]

The randomized, open-label, phase III KEYLYNK-010 (ClinicalTrials.gov identifier: NCT03834519) study evaluated efficacy and safety of pembrolizumab plus olaparib versus NHA switch in participants with biomarker-unselected mCRPC that progressed on abiraterone or enzalutamide (but not both) and docetaxel.

METHODS

Study Design

The KEYLYNK-010 study was conducted at 193 study sites across six regions. The Protocol (online only) and all amendments were approved by the appropriate ethics committees at each center. The study was conducted in accordance with Good Clinical Practice guidelines. An external data monitoring committee (eDMC) oversaw the study and assessed interim results. All participants provided written informed consent.

Eligible participants were male, age 18 years and older, and had histologically or cytologically confirmed mCRPC not preselected for HRR gene alterations that was progressing during continued ADT (serum testosterone <50 ng/dL) as

determined by prostate-specific antigen (PSA) levels, radiographically by RECIST 1.1, or radiographically in bone by Prostate Cancer Working Group (PCWG). Participants had an Eastern Cooperative Oncology Group performance status of ≤1, adequate organ function, prior abiraterone acetate (either for mHSPC or mCRPC) or enzalutamide (for mCRPC), but not both, and disease progression during or after prior docetaxel. Tissue and blood samples for exploratory biomarker analysis and genetic testing were collected prospectively at screening. Testing occurred after study initiation (Data Supplement [Methods], online only).

Participants were randomly assigned (2:1), stratified by prior NHA (abiraterone *v* enzalutamide) and presence of measurable disease at baseline (yes *v* no), to receive 200 mg pembrolizumab intravenously once every 3 weeks (for ≤35 cycles) plus 300 mg olaparib orally twice daily, or 1,000 mg abiraterone acetate orally once daily plus 5 mg prednisone/prednisolone orally twice daily (if prior enzalutamide) or 160 mg enzalutamide orally once daily (if prior abiraterone). Neither participants nor investigators were blinded to treatment assignment. Participants discontinued study treatment upon request at any time for any reason, or because of verified radiographic disease progression, intercurrent illness, prolonged treatment interruption, unacceptable toxicity, investigator's decision to discontinue therapy, protocol noncompliance, or completion of 35 cycles of pembrolizumab. Pembrolizumab interruptions or discontinuations were permitted. Twice-daily olaparib could be dose-reduced to 250 mg, and then to 200 mg, followed by discontinuation. Re-escalation of the olaparib dose was not permitted.

Efficacy and safety assessment methods are provided in the Data Supplement.

End Points

Dual primary end points were radiographic PFS (rPFS) per PCWG-modified RECIST 1.1 by blinded independent central review (BICR) and OS (definitions provided in the Data Supplement). Time to first subsequent therapy (TFST) was a key secondary end point. Secondary end points included objective response rate (ORR) and duration of response (DOR) per PCWG-modified RECIST 1.1 by BICR, time to PSA progression, and safety.

Statistical Analysis

Efficacy was assessed in all randomly assigned participants (intention-to-treat [ITT] population). Safety was assessed in all randomly assigned participants who received ≥1 dose of study treatment (as-treated population). Event rates over time for rPFS, OS, TFST, and time to PSA progression were estimated by the nonparametric Kaplan-Meier method. HRs and 95% CI were estimated with a Cox regression model (stratified by prior NHA therapy [abiraterone *v* enzalutamide] and measurable disease at baseline [yes *v* no]) with Efron's method of tie handling and treatment group as the single covariate. Between-treatment differences were evaluated using a log-rank test with the same stratification factors. Planned study sample size was approximately 780 participants (approximately 520 to pembrolizumab plus olaparib and approximately 260 to NHA). The study had approximately 90% power to detect superior OS with pembrolizumab plus olaparib over NHA with HR = 0.725 with approximately 482 OS events at an initial overall α = .02 (one-sided), and approximately 90% power to detect superior rPFS (HR, 0.65) with approximately 360 rPFS events at an initial overall α = .005 (one-sided). The overall type-I error rate was strongly controlled at 2.5% (one-sided) using the Maurer and Bretz graphical method,[19] with 2.0% and 0.5% allocated to test OS and rPFS, respectively. No initial α was allocated to TFST, planned to be tested only if the rPFS null hypothesis was rejected. Statistical testing for rPFS was conducted at the first protocol-specified interim analysis (IA1), planned to occur after ≥360 rPFS events and ≥241 deaths (Data Supplement [Table S1]). This study was stopped for futility after the second interim analysis (IA2) per the eDMC and final testing for OS occurred at IA2 after ≥386 OS events. The *P* value boundary for significance was .005 (one-sided) for rPFS and .0093 (one-sided) for OS.

SAS software, version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses. The full statistical analysis plan is provided in the protocol (Data Supplement).

RESULTS

Between May 30, 2019, and July 16, 2021, 793 participants were randomly assigned to receive pembrolizumab plus olaparib (n = 529) or NHA (n = 264; Fig 1). Baseline characteristics were balanced between arms (Table 1). HRR mutations and BRCA mutations were detected in 138 (26.1%) and 52 (9.8%) participants in the pembrolizumab plus olaparib arm and in 59 (22.3%) and 24 (9.1%) participants in the NHA arm, respectively. One hundred twenty-seven (24.0%) and 50 (18.9%) participants in each arm, respectively, had mCRPC with PD-L1 combined positive score (CPS) ≥1. Among 316 participants with evaluable samples, 6 (1.9%) had MSI-high status; no further analysis was performed on this subgroup. The median time from random assignment to the data cutoff date (July 19, 2021) was 12.7 months (range, 0.1-25.7) at IA1, and 18.7 months (range, 6.1-31.7) at IA2 (data cutoff date, January 18, 2022). The median number of doses of pembrolizumab was 7.0 (range, 1-35). Median average daily doses of olaparib, abiraterone, or enzalutamide were 595.7 mg (range, 212-600), 1,000.0 mg (range, 643-1,200), and 160.0 mg (range, 96-160), respectively. Among the ITT population at IA2, 272 (51.4%) participants in the pembrolizumab plus olaparib arm and 146 (55.3%) participants in the NHA arm had received subsequent anticancer therapy (Data Supplement [Tables S2A and S2B]), most commonly cabazitaxel (n = 197 [37.2%] and n = 108 [40.9%], respectively).

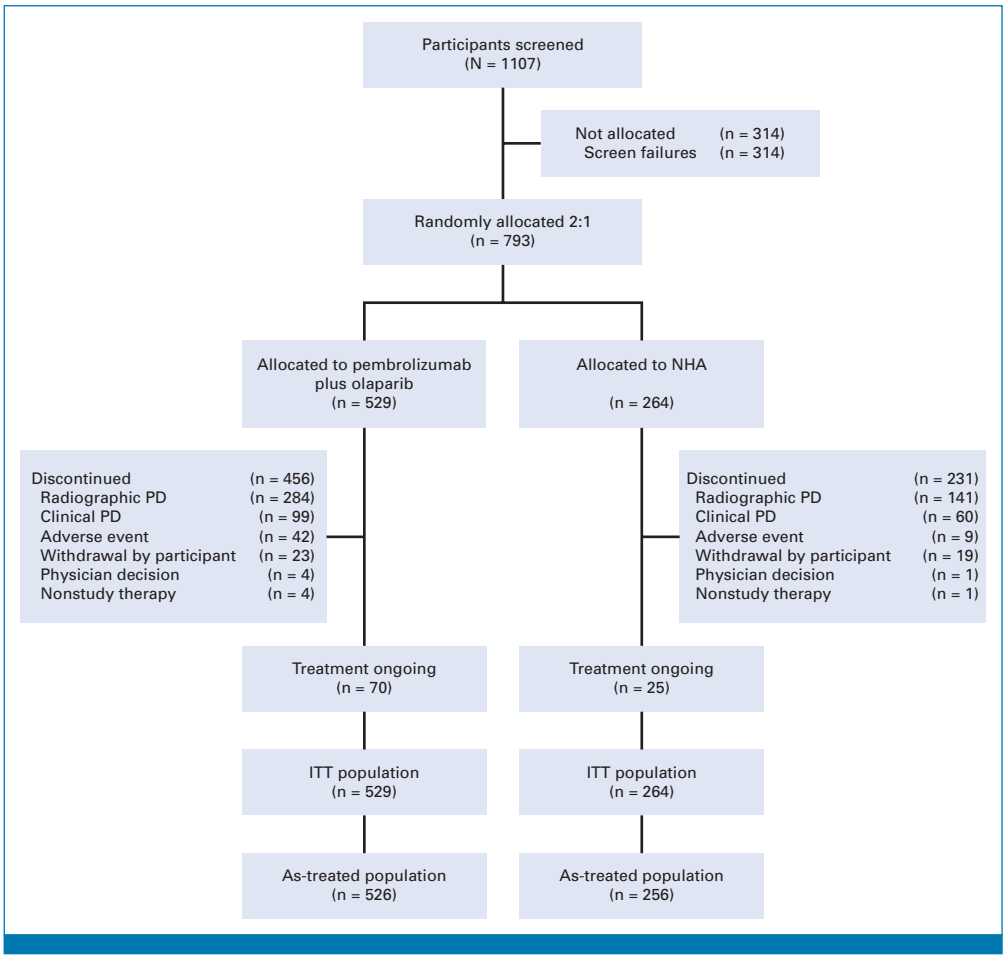

FIG 1. CONSORT diagram. ITT, intention-to-treat; NHA, next-generation hormonal agent; PD, progressive disease.

At IA1, 291 (55.0%) rPFS events had occurred in the pembrolizumab plus olaparib arm and 128 (48.5%) had occurred in the NHA arm. Median rPFS was 4.4 months (95% CI, 4.2 to 6.0) with pembrolizumab plus olaparib and 4.2 months (95% CI, 4.0 to 6.1) with NHA (HR, 1.02 [95% CI, 0.82 to 1.25]; $P = .5544$; Fig 2A). Estimated rPFS rate at 12 months was 16.3% (95% CI, 11.8 to 21.3) and 21.1% (95% CI, 14.1 to 29.1), respectively. Similar results were observed at IA2 (median rPFS, 4.6 months [95% CI, 4.2 to 6.0] *v* 4.2 months [95% CI, 4.0 to 6.1]; HR, 0.96, 95% CI, 0.79 to 1.16; Data Supplement [Fig S1A]). After 293 (55.4%) deaths in the pembrolizumab plus olaparib arm and 149 (56.4%) deaths in the NHA arm at IA2, the median OS was 15.8 months (95% CI, 14.6 to 17.0) versus 14.6 months (95% CI, 12.6 to 17.3; HR, 0.94 [95% CI, 0.77 to 1.14]; $P = .2616$; Fig 2B). Estimated OS rate at 12 months was 64.3% (95% CI, 59.9 to 68.5) versus 59.4% (95% CI, 52.9 to 65.4), respectively. Subgroup analyses of rPFS at IA1 and OS at IA2 are shown in Figures 3A and 3B. rPFS and OS results were generally consistent across subgroups, including PD-L1 status, with HRs for rPFS and OS of 1.07 (95% CI, 0.84 to 1.35) and 0.94 (95% CI, 0.75 to 1.19) in participants with CPS <1 and 1.03 (95% CI, 0.65 to 1.63) and 0.90 (95% CI, 0.59 to 1.37) in participants with CPS ≥1, respectively. Among participants with HRR mutations, the HRs for rPFS and OS were 0.69 (95% CI, 0.46 to 1.03) and 0.88 (95% CI, 0.59 to 1.33), respectively. Among participants with BRCA mutations, the HRs for rPFS and OS were 0.40 (95% CI, 0.21 to 0.79) and 0.52 (95% CI, 0.27 to 0.99), respectively.

At IA1, 329 (62.2%) and 169 (64.0%) TFST events had occurred in the pembrolizumab plus olaparib and NHA arms, respectively. The median TFST was 7.2 months (95% CI, 6.7 to 8.1) versus 5.7 months (95% CI, 5.0 to 7.1), respectively (HR, 0.86 [95% CI, 0.71 to 1.03]; Fig 4). Since neither the rPFS nor OS dual primary end points were met, TFST was not formally statistically tested. Estimated TFST at 12 months was 28.8% (95% CI, 24.7 to 32.9) with pembrolizumab plus olaparib and 26.8% (95% CI, 21.4 to 32.6) with NHA at IA2. Two hundred forty-four (46.1%) participants in the pembrolizumab plus olaparib arm and 119 (45.1%) participants in the NHA arm had measurable disease and were evaluable for ORR at IA2. A complete or partial response occurred in 41 and in seven participants, respectively, with an ORR of 16.8% (95% CI, 12.3 to 22.1) and

TABLE 1. Baseline Characteristics and Demographics in the Intention-to-Treat Population

Characteristic	Pembrolizumab Plus Olaparib (n = 529)	NHA (n = 264)
Age, years, median (range)	71.0 (40-89)	69.0 (49-84)
≥65, No. (%)	411 (77.7)	194 (73.5)
ECOG performance status, No. (%)		
0	255 (48.2)	139 (52.7)
1	272 (51.4)	125 (47.3)
2	2 (0.4)	0
Geographic location, No. (%)		
North America	43 (8.1)	27 (10.2)
Western Europe	222 (42.0)	112 (42.4)
Rest of world	264 (49.9)	125 (47.3)
Race, No. (%)		
American Indian or Alaska Native	1 (0.2)	0
Asian	102 (19.3)	59 (22.3)
Black or African American	1 (0.2)	4 (1.5)
Multiple	1 (0.2)	0
Native Hawaiian or other Pacific Islander	1 (0.2)	1 (0.4)
White	419 (79.2)	199 (75.4)
Missing	4 (0.8)	1 (0.4)
Prior NHA treatment, No. (%)		
Abiraterone only	289 (54.6)	143 (54.2)
Enzalutamide only	240 (45.4)	120 (45.5)
Abiraterone and enzalutamide[a]	0	1 (0.4)
Prior chemotherapy, No. (%)		
Docetaxel only	519 (98.1)	258 (97.7)
Cabazitaxel only[a]	1 (0.2)	0
Docetaxel and cabazitaxel	6 (1.1)	4 (1.5)
Other[a]	3 (0.6)	2 (0.8)
Disease measurable by RECIST 1.1, No. (%)	244 (46.1)	119 (45.1)
PSA value median (range), ng/mL, No. (%)	52.9 (0.1-5,000.0)	42.6 (0.1-4, 007.0)
Gleason sum, No. (%)		
≤7 (grade groups 1-3)	147 (27.8)	69 (26.1)
≥8 (grade groups 4-5)	367 (69.4)	184 (69.7)
Unknown	15 (2.8)	11 (4.2)
Type of metastasis at baseline, No. (%)		
Bone only	221 (41.8)	112 (42.4)
Liver	50 (9.5)	34 (12.9)
Other	258 (48.8)	118 (44.7)
HRR gene alteration status, No. (%)		
HRR-mutated	138 (26.1)	59 (22.3)
Non–HRR-mutated	355 (67.1)	173 (65.5)
Unknown	36 (6.8)	32 (12.1)
BRCA mutational status, No. (%)		
BRCA-mutated	52 (9.8)	24 (9.1)
Non–BRCA-mutated	441 (83.4)	208 (78.8)
Unknown	36 (6.8)	32 (12.1)
PD-L1 CPS,[b] No. (%)		
CPS <1	365 (69.0)	197 (74.6)
CPS ≥1	127 (24.0)	50 (18.9)
Not evaluable/unknown	37 (7.0)	17 (6.4)

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; NHA, next-generation hormonal agent; PSA, prostate-specific antigen.
[a]Protocol deviation. Other therapies included carboplatin or no prior chemotherapy.
[b]The PD-L1 CPS was 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.

5.9% (95% CI, 2.4 to 11.7; Table 2). Median DOR was 8.1 months (range, ≥1.9 to ≥24.2) with pembrolizumab plus olaparib and 8.5 months (range, ≥2.0 to 14.7) with NHA. At IA2, median time to PSA progression was 3.3 months (95% CI, 3.0 to 3.5) versus 3.5 months (95% CI, 3.2 to 4.3), respectively (HR, 1.11 [95% CI, 0.89 to 1.38]; Data Supplement [Fig S2]). PSA response (defined as ≥50% decrease in PSA levels from baseline among participants with available baseline PSA) was observed in 83/501 (16.6%; 95% CI, 13.4 to 20.1) and 47/247 (19.0%; 95% CI, 14.3 to 24.5) participants in the pembrolizumab plus olaparib versus NHA arms.

The as-treated population included 526 participants who received ≥1 dose of pembrolizumab plus olaparib and 256 participants who received ≥1 dose of NHA. The median duration (range) of therapy was 5.0 months (0.2-28.9) and 4.1 months (0.4-28.8), respectively. One hundred sixty-four (31.2%) participants had ≥1 olaparib dose reduction; 52 (9.9%) had two reductions. At least one any-grade, any-cause adverse event (AE) occurred in 516 (98.1%) and 237 (92.6%) participants in the pembrolizumab plus olaparib and NHA arms, and grade 3-5 any-cause AEs occurred in 301 (57.2%) and 101 (39.5%) participants, respectively (Table 3). In the pembrolizumab plus olaparib arm, 80 (15.2%) participants discontinued treatment and 21 (4.0%) participants died due to any-cause AEs. In the NHA arm, 9 (3.5%) participants discontinued treatment and 6 (2.3%) died due to any-cause AEs. Reasons for discontinuation for each drug and AEs resulting in death are provided in the Data Supplement ([Tables S3 and S4]). One hundred sixty-eight (31.9%) and 55 (21.5%) participants who received pembrolizumab plus olaparib versus NHA experienced ≥1 any-cause serious AE (Data Supplement [Table S5]), most commonly anemia (n = 18; 3.4%), pneumonia (n = 15; 2.9%),

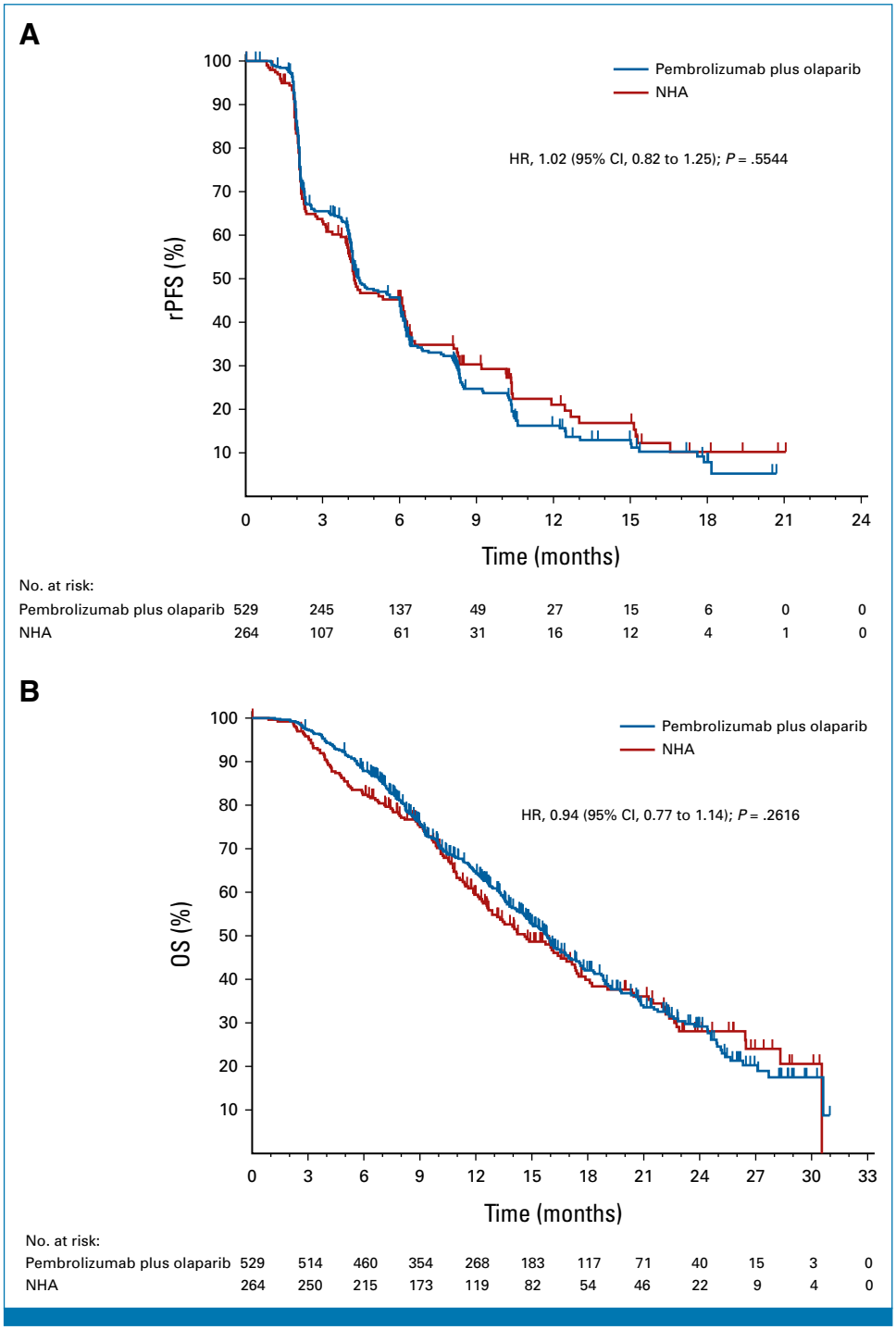

FIG 2. rPFS and OS in the intention-to-treat population. Kaplan-Meier estimates of (A) rPFS per PCWG-modified RECIST 1.1 by blinded independent central review at the first interim analysis and (B) OS at the second interim analysis in the trial groups. Tick marks indicate censored observations. HR, hazard ratio; NHA, next-generation hormonal agent; OS, overall survival; PCWG, Prostate Cancer Working Group; rPFS, radiographic progression-free survival.

urinary tract infection (n = 10; 1.9%), and adrenal insufficiency (n = 9; 1.7%) with pembrolizumab plus olaparib and urinary tract infection (n = 4; 1.6%), hematuria (n = 4; 1.6%), anemia (n = 3; 1.2%), hyponatremia (n = 3; 1.2%), and pyelonephritis (n = 3; 1.2%) with NHA.

A total of 464 (88.2%) participants with pembrolizumab plus olaparib and 130 (50.8%) participants with NHA had ≥1 any-grade treatment-related AE (Table 3). Grade 3-5 treatment-related AEs occurred in 182 (34.6%) participants with pembrolizumab plus olaparib, including four

deaths (0.8%; one each due to immune-mediated hepatitis, pneumonia, craniocerebral injury, and renal failure). Grade 3-4 treatment-related AEs occurred in 23 (9.0%) participants with NHA, with no treatment-related deaths.

Any-grade and grade 3-5 immune-mediated AEs occurred, respectively, in 95 (18.1%) and 27 (5.1%) participants with pembrolizumab plus olaparib, including one grade 5 event (hepatitis), and in 14 (5.5%) and 3 (1.2%) participants with NHA (Data Supplement [Table S6]). Seventeen (3.2%) participants in the pembrolizumab plus olaparib arm and none in the NHA arm received high-dose (≥40 mg/d) systemic corticosteroids for immune-mediated AEs and infusion reactions.

DISCUSSION

The phase III KEYLYNK-010 study did not show a statistically significant improvement in rPFS or OS with pembrolizumab plus olaparib versus the active comparator NHA in participants with biomarker-unselected, previously treated mCRPC. The study was stopped for futility after IA2 on the basis of guidance from the eDMC. Although not formally tested per the prespecified multiplicity strategy, TFST analysis suggested that pembrolizumab plus olaparib may delay the need for next-line therapy versus NHA. In line with previous observations,[17] pembrolizumab plus olaparib demonstrated antitumor activity, with a higher ORR than NHA in the ITT population with measurable disease. Subgroup

A rPFS (Interim Analysis 1)

Subgroup	Events/Participants: Pembrolizumab + Olaparib	Events/Participants: NHA	HR (95% CI)	Median (95% CI): Pembrolizumab + Olaparib	Median (95% CI): NHA
Overall	291/529	128/264	1.02 (0.82 to 1.25)	4.4 (4.2 to 6.0)	4.2 (4.0 to 6.1)
Age, years					
<65	68/118	27/70	1.13 (0.72 to 1.77)	4.2 (4.1 to 6.0)	6.1 (2.1 to 8.3)
≥65	223/411	101/194	1.02 (0.80 to 1.29)	4.5 (4.2 to 6.0)	4.2 (3.9 to 6.1)
Race					
White	235/418	95/199	1.06 (0.84 to 1.35)	4.4 (4.2 to 6.0)	4.2 (3.2 to 6.2)
All others	55/107	33/64	0.93 (0.60 to 1.43)	5.5 (4.0 to 6.2)	4.2 (3.9 to 6.2)
ECOG PS					
0	137/257	63/139	1.12 (0.83 to 1.51)	5.2 (4.2 to 6.2)	6.1 (4.0 to 6.6)
≥1	154/272	65/125	0.94 (0.71 to 1.26)	4.2 (4.0 to 5.6)	4.1 (2.7 to 6.1)
Measurable disease at baseline					
Yes	164/242	73/118	0.81 (0.61 to 1.07)	4.1 (3.7 to 4.3)	3.1 (2.2 to 4.2)
No	127/287	55/146	1.25 (0.91 to 1.72)	6.1 (4.6 to 6.4)	8.1 (6.1 to 10.3)
Prior NHA treatment					
Abiraterone only	156/289	67/143	1.04 (0.78 to 1.39)	4.4 (4.1 to 6.1)	4.2 (3.9 to 6.2)
Enzalutamide only	135/240	60/120	1.03 (0.76 to 1.39)	4.5 (4.1 to 6.0)	4.3 (3.4 to 6.2)
Region					
North America	23/43	11/27	0.68 (0.33 to 1.42)	4.1 (2.3 to 10.3)	2.3 (2.1 to 4.2)
Outside North America	268/486	117/237	1.07 (0.86 to 1.32)	4.4 (4.2 to 6.0)	4.4 (4.0 to 6.2)
HRR gene alteration status					
HRR-mutated	71/138	37/59	0.69 (0.46 to 1.03)	6.3 (4.2 to 8.3)	3.9 (2.2 to 4.2)
Non–HRR-mutated	201/355	81/173	1.26 (0.98 to 1.64)	4.2 (4.0 to 4.7)	5.4 (4.0 to 6.4)
Unknown	19/36	10/32	0.81 (0.37 to 1.77)	6.2 (4.0 to 10.5)	6.1 (2.1 to 6.4)
BRCA mutational status					
BRCA-mutated	23/52	15/24	0.40 (0.21 to 0.79)	8.4 (6.3 to 10.5)	2.7 (2.0 to 4.0)
Non–BRCA-mutated	249/441	103/208	1.20 (0.95 to 1.51)	4.2 (4.1 to 4.5)	4.4 (4.0 to 6.3)
Unknown	19/36	10/32	0.81 (0.37 to 1.77)	6.2 (4.0 to 10.5)	6.1 (2.1 to 6.4)
PD-L1 status					
CPS <1	202/372	101/202	1.07 (0.84 to 1.35)	4.3 (4.1 to 5.6)	4.4 (4.0 to 6.2)
CPS ≥1	74/127	24/52	1.03 (0.65 to 1.63)	4.4 (4.0 to 6.4)	3.9 (2.1 to 6.6)

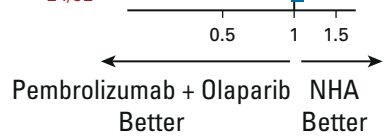

FIG 3. Subgroup analysis of rPFS and OS in the intention-to-treat population. Analysis of (A) rPFS per PCWG-modified RECIST 1.1 by blinded independent central review at the first interim analysis and (B) OS at the second interim analysis in key prespecified subgroups. CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRR, homologous recombination repair; NHA, next-generation hormonal agent; NR, not reached; OS, overall survival; PCWG, Prostate Cancer Working Group; PS, performance status; rPFS, radiographic progression-free survival. (continued on following page)

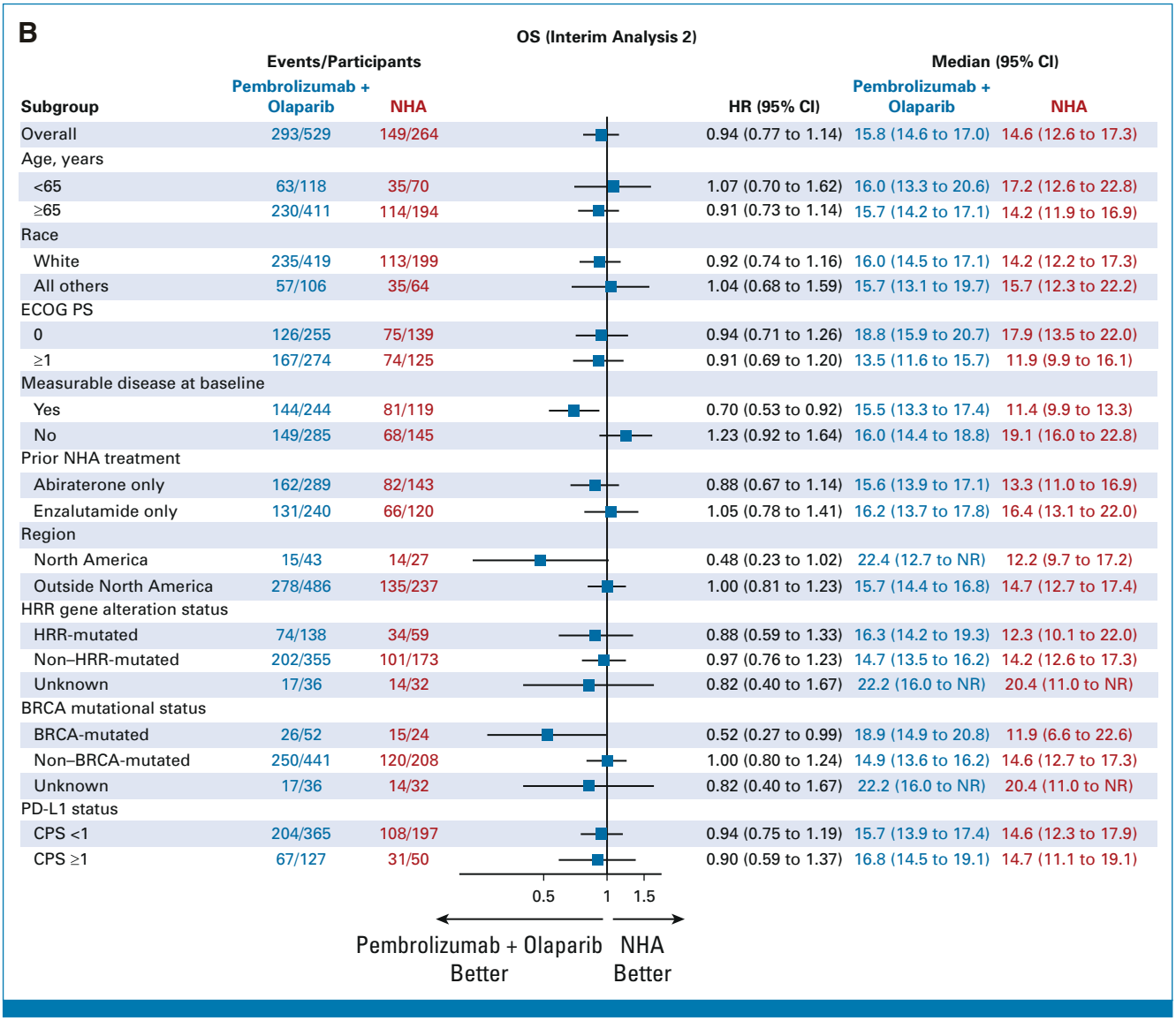

FIG 3. (Continued).

analysis suggested a possible rPFS and OS benefit with pembrolizumab plus olaparib versus NHA in these participants. rPFS and OS outcomes were consistent with each regimen irrespective of tumor PD-L1 CPS.

The frequency of HRR gene alterations was 24.8% in the ITT population, consistent with prior observations using similar sequencing methods such as the PROpel (28.4% in the ITT population) and PROfound (28% among screened patients) studies.[13,20] BRCA mutations were detected in 9.6% of the ITT population in KEYLYNK-010, similar to the frequency reported in PROpel (*BRCA1* mutation rate, 1.5%; *BRCA2* mutation rate, 9.2%).[13] In KEYLYNK-010, rPFS and OS results favored pembrolizumab plus olaparib over NHA in the subset of participants with BRCA mutations, and similar (although less pronounced) trends were observed in the broader population with all HRR mutations. No formal statistical testing was prespecified or performed for these subgroups and no definitive conclusions could be drawn. This result was consistent with expectations on the basis of the known susceptibility of HRR-mutated and BRCA-mutated prostate cancers to PARP inhibition.[13,20]

More serious AEs, AEs leading to therapy discontinuation, and treatment-related AEs of any grade and grade ≥3 occurred with pembrolizumab plus olaparib versus NHA. The safety profile of pembrolizumab plus olaparib was consistent with prior observations and no new safety signals were observed.[18,20,21]

Efficacy findings for pembrolizumab plus olaparib in KEYLYNK-010 were consistent with reports from the biomarker-unselected population in Cohort A of KEYNOTE-365 (median rPFS, 4.5 months [95% CI, 4.0 to 6.5]; median

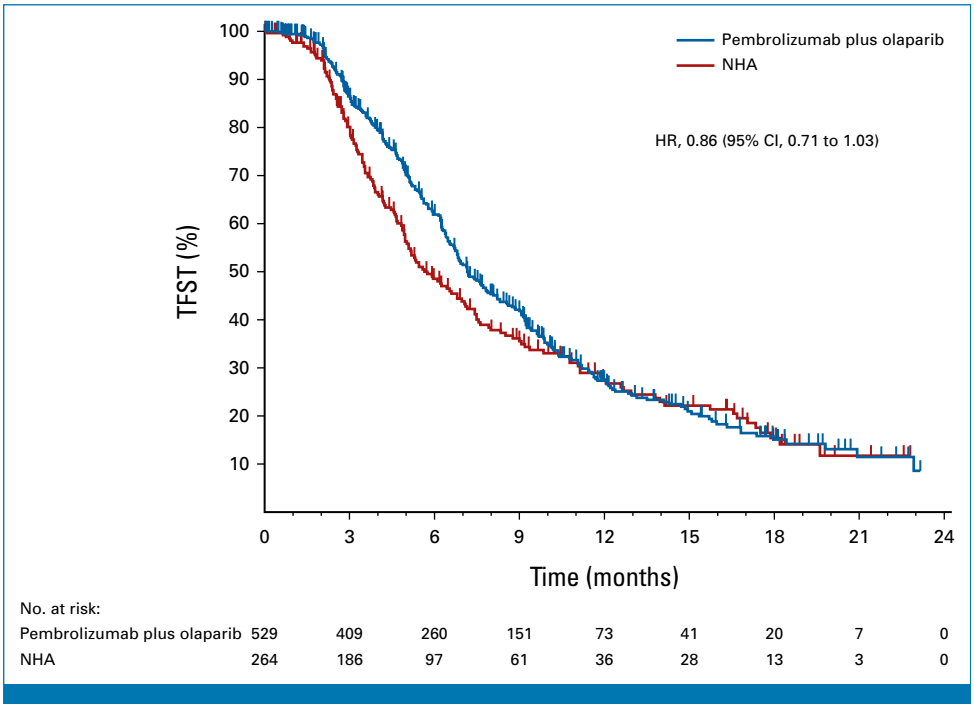

FIG 4. TFST in the intention-to-treat population. Kaplan-Meier estimates of TFST at the first interim analysis in the trial groups. Tick marks indicate censored observations. HR, hazard ratio; NHA, next-generation hormonal agent; TFST, time to first subsequent therapy.

OS, 14 months [95% CI, 10.4 to 18.2]).[18] Outcomes for participants in the NHA arm were generally better than expected on the basis of historical observations. Although direct comparisons between trials cannot be made, the randomized, phase IV CARD study investigated cabazitaxel versus NHA switch in a population somewhat similar to KEYLYNK-010, that is, participants with mCRPC that progressed during 12 months of treatment with one prior NHA before or after ≥3 cycles of prior docetaxel. The median imaging-based PFS was 3.7 months (95% CI, 2.8 to 5.1) and median OS was 11.0 months (95% CI, 9.2 to 12.9) with NHA in CARD.[5] Cabazitaxel demonstrated promising efficacy in CARD and was the most common subsequent anticancer therapy in KEYLYNK-010. Cabazitaxel's widespread use after NHA failure may partly account for the prolonged survival observed in our study. In the contemporaneous phase III VISION study, participants with PSMA-positive mCRPC with ≥1 prior NHA and 1-2 prior taxane regimens were randomly assigned to standard-of-care versus standard-of-care plus ^{177}Lu-PSMA-617.[3] More than 40% of participants had received two prior NHAs and more than 40% had received two prior taxanes. Therefore, the VISION population was more heavily pretreated than the KEYLYNK-010 and CARD populations but had a median imaging-based PFS of 8.7 months and median OS of 15.3 months in the ^{177}Lu-PSMA-617 arm versus 3.4 months and 11.3 months with standard-of-care.[3,5] Although few participants in the KEYLYNK-010 study received subsequent radiopharmaceutical therapy (approximately 7% in the pembrolizumab plus olaparib arm and approximately 10% in the NHA arm), the evolving later-line treatment landscape may result in better outcomes for control groups in future mCRPC studies compared with historical controls. These data should prove informative for future trial design assumptions, statistics, and sample size planning.

TABLE 2. Best Overall Response by BICR Per PCWG-Modified RECIST 1.1 in the Intention-to-Treat Population With Measurable Disease at Baseline

Parameter	Pembrolizumab Plus Olaparib (n = 244), No. (%)	NHA (n = 119), No. (%)
Objective response rate	41 (16.8)	7 (5.9)
95% CI	12.3 to 22.1	2.4 to 11.7
Best overall response		
Complete response	4 (1.6)	0
Partial response	37 (15.2)	7 (5.9)
Stable disease	107 (43.9)	52 (43.7)
Progressive disease	88 (36.1)	45 (37.8)
Nonevaluable[a]	3 (1.2)	2 (1.7)
No assessment[b]	5 (2.0)	13 (10.9)
Disease control rate[c]	79 (32.4)	23 (19.3)
95% CI	26.5 to 38.6	12.7 to 27.6

Abbreviations: BICR, blinded independent central review; NHA, next-generation hormonal agent; PCWG, Prostate Cancer Working Group.
[a]Postbaseline assessment(s) available, but not evaluable.
[b]No postbaseline assessment available for response evaluation.
[c]Complete response plus partial response plus stable disease for ≥6 months.

TABLE 3. Summary of Treatment-Related AEs in the As-Treated Population

AE	Pembrolizumab Plus Olaparib (n = 526), No. (%)	NHA (n = 256), No. (%)
Any	464 (88.2)	130 (50.8)
Grade 3-5	182 (34.6)	23 (9.0)
Leading to discontinuation of treatment	57 (10.8)	4 (1.6)
Leading to death	4 (0.8)	0

Treatment-Related AEs With Incidence ≥5%	Any Grade, No. (%)	Grade 3-5, No. (%)	Any Grade, No. (%)	Grade 3-5, No. (%)
Anemia	242 (46.0)	103 (19.6)	7 (2.7)	3 (1.2)
Nausea	187 (35.6)	8 (1.5)	13 (5.1)	0
Fatigue	135 (25.7)	16 (3.0)	42 (16.4)	4 (1.6)
Decreased appetite	112 (21.3)	7 (1.3)	12 (4.7)	1 (0.4)
Asthenia	71 (13.5)	12 (2.3)	18 (7.0)	1 (0.4)
Diarrhea	66 (12.5)	4 (0.8)	6 (2.3)	1 (0.4)
Vomiting	65 (12.4)	4 (0.8)	4 (1.6)	0
Hypothyroidism	47 (8.9)	1 (0.2)	2 (0.8)	0
Dysgeusia	29 (5.5)	0	2 (0.8)	0
Rash	27 (5.1)	1 (0.2)	0	0
Hypertension	2 (0.4)	1 (0.2)	13 (5.1)	6 (2.3)
Hot flush	1 (0.2)	0	13 (5.1)	0

NOTE. The as-treated population was defined as all participants who received ≥1 dose of study treatment.
Abbreviations: AE, adverse event; NHA, next-generation hormonal agent.

A potential limitation of the KEYLYNK-010 design was differing treatment practices for the broad population of patients with biomarker-unselected mCRPC across geographic regions. The study was not powered to formally test for ORR superiority in the ITT population or rPFS or OS superiority in subgroups, and some subgroup sizes were small. Biomarker analysis outside the scope of this report may help identify patients who could benefit from immunotherapy plus PARP inhibition.

Although immune checkpoint inhibitors have shown single-agent activity in select patients with prostate cancer, multiple phase III trials of anti-PD-(L)1 antibody monotherapies or combinations have reported negative results. KEYLYNK-010 underscores the challenges of an immunosuppressive prostate TME characterized by myeloid-derived suppressor cells, M2 macrophages, and suppressive cytokines such as transforming growth factor–beta.[6-8,22] Combinations that potentially modulate the TME may be a future approach in mCRPC. Adding an anti–T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains antibody to anti-PD-1 therapy could enhance cluster of differentiation 8+ T- and natural killer–cell antitumor activity and alleviate the immunosuppressive effect of tumor-infiltrating regulatory T cells.[23-25] Anti-PD-1 antibodies combined with multikinase inhibitors such as cabozantinib or lenvatinib that block myeloid-derived suppressor cells involved in tumor immune evasion are also being explored.[26,27] Finally, ongoing efforts to better characterize immunologic parameters and tumoral molecular features may help refine patient selection for immunotherapy.[28] With median OS estimates of only 11-15 months, a clear unmet need remains for additional effective treatment options for previously treated mCRPC,[3,5] and studies are continually exploring how to best deploy immune checkpoint antibodies in the prostate cancer treatment continuum.

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DATA SHARING STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (MSD), 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 United States and European Union 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.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab Plus Olaparib for Patients With Previously Treated and Biomarker-Unselected Metastatic Castration-Resistant Prostate Cancer: The Randomized, Open-Label, Phase III KEYLYNK-010 Trial

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