ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Pembrolizumab plus enzalutamide and androgen deprivation therapy versus placebo plus enzalutamide and androgen deprivation therapy for metastatic hormone-sensitive prostate cancer: the randomized, double-blind, phase III KEYNOTE-991 study☆

C. Gratzke[1*], M. Özgüroğlu[2], A. Peer[3], M. A. N. Sendur[4], M. Retz[5], J. C. Goh[6], W. Loidl[7], G. Jayram[8], S.-S. Byun[9], C. Kwak[10], M. Kwiatkowski[11], R. Manneh Kopp[12], J. C. V. Limón[13,14], J. F. E. Penagos[15], U. De Giorgi[16], K. M. da Trindade[17], C. Niu[18], Y. Liu[19], C. H. Poehlein[19] & J. M. Piulats[20]

[1]Department of Urology, University Hospital Freiburg, Freiburg, Germany; [2]Division of Medical Oncology, Department of Internal Medicine, Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Istanbul, Turkey; [3]Department of Oncology, Rambam Medical Center, Haifa, Israel; [4]Department of Medical Oncology, Ankara Yildirim Beyazit University Faculty of Medicine and Ankara Bilkent City Hospital, Ankara, Turkey; [5]Department of Urology, Rechts der Isar Medical Center, Technical University Munich, Munich, Germany; [6]Gallipoli Medical Research—Greenslopes Private Hospital, Greenslopes, Australia; [7]Department of Urology and Andrology, Ordensklinikum Linz GmbH Elisabethinen, Linz, Austria; [8]Urology Associates P.C., Nashville, USA; [9]Department of Urology, Seoul National University Bundang Hospital, Seongnam; [10]Department of Urology, Seoul National University Hospital, Seoul, Republic of Korea; [11]Oddział Dzienny Chemioterapii, Szpital Wojewódzki im. Mikołaja Kopernika, Koszalin, Poland; [12]Sociedad de Oncología y Hematología del Cesar S.A.S., Valledupar, Colombia; [13]Hospital Civil de Guadalajara "Fray Antonio Alcalde", Guadalajara; [14]Universidad de Guadalajara, Guadalajara; [15]Hospital San Lucas Cardiología del Sureste, Tuxtla Gutiérrez, México; [16]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [17]Instituto D'Or de Pesquisa e Ensino, Brazil and Latin American Cooperative Oncology Group, Brazil; [18]MSD China, Beijing, China; [19]Merck & Co., Inc., Rahway, USA; [20]Instituto Catalan de Oncologia—IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

Available online 16 May 2025

Background: Despite treatment advances, most patients with metastatic hormone-sensitive prostate cancer (mHSPC) experience disease progression to castration-resistant disease within 5 years. The placebo-controlled, double-blind, phase III KEYNOTE-991 study evaluated the efficacy and safety of adding pembrolizumab to enzalutamide and androgen deprivation therapy (ADT) in participants with mHSPC.

Patients and methods: Eligible participants were aged ≥18 years with next-generation hormonal agent-naive mHSPC. Participants were randomly assigned (1 : 1) to receive intravenous pembrolizumab 200 mg or placebo every 3 weeks for ≤35 cycles, with oral enzalutamide 160 mg and continuous ADT. Primary endpoints were radiographic progression-free survival (rPFS) and overall survival (OS). Safety was a secondary endpoint.

Results: Between 2 March 2020 and 9 August 2021, 626 participants were randomly assigned to receive pembrolizumab plus enzalutamide and ADT and 625 participants to receive placebo plus enzalutamide and ADT. At the first interim analysis, the median follow-up was 21.1 months (range 14.8-32.0 months). rPFS was not superior with pembrolizumab versus placebo [median not reached in both arms; hazard ratio (HR) 1.20, 95% confidence interval (CI) 0.96-1.49, $P = 0.9467$]. Median OS was not reached in either arm (HR 1.16, 95% CI 0.88-1.53; not formally statistically tested as per the multiplicity strategy). Grade ≥3 adverse events (AEs) and serious AEs (SAEs) were reported in 61.9% versus 38.1% and 40.3% versus 23.2% of participants in the pembrolizumab versus the placebo arm, respectively. Any-grade rash occurred at a higher frequency with pembrolizumab (25.1%) versus placebo (9.3%).

Conclusions: KEYNOTE-991 did not meet its primary endpoint and was stopped for futility. The addition of pembrolizumab to enzalutamide and ADT was associated with higher frequencies of grade ≥3 AEs and SAEs than with placebo. Rash was identified as an additional safety signal with pembrolizumab plus enzalutamide and ADT.

Key words: androgen deprivation therapy, combination therapy, metastatic hormone-sensitive prostate cancer, pembrolizumab, PD-1 inhibitor

*Correspondence to: Dr Christian Gratzke, Department of Urology, University Hospital Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany. Tel: +49-761-270-28910; Fax: +49-761-270-28780

E-mail: christian.gratzke@uniklinik-freiburg.de (C. Gratzke).

☆Note: The data were previously presented in part at the European Society for Medical Oncology (ESMO) Congress (20-24 October 2023).

INTRODUCTION

Metastatic hormone-sensitive prostate cancer (mHSPC) historically has been treated with androgen deprivation therapy (ADT) with the aim of controlling the disease for as long as possible. The addition of a next-generation hormonal agent (NHA) to ADT has improved outcomes for this patient population and is the current standard of care.[1-3] Patients can also receive an intensified triple regimen with ADT, NHA, and docetaxel.[3] Nevertheless, up to half of the participants in the phase III studies that established these treatment combinations (ARCHES, PEACE-1, STAMPEDE, ARASENS, TITAN) developed castration-resistant disease within 5 years.[4-7] Therefore, new therapeutic options are needed to further delay disease progression and improve survival rates.

In the clinical setting, combination therapy with the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab and NHA has demonstrated antitumor activity in patients with metastatic castration-resistant prostate cancer (mCRPC), including in cohorts 4 and 5 of the phase II KEYNOTE-199 study and cohort C of the phase Ib/II KEYNOTE-365 study.[8,9] The safety profile of this combination was generally consistent with the safety profiles of the individual agents, except for a high incidence of any-grade treatment-related rash (KEYNOTE-199: 14.3%; KEYNOTE-365: 22%).[8,9]

Clinical trial data from patients with mHSPC treated with pembrolizumab are limited to a single-center pilot study of 12 participants with oligometastatic HSPC who underwent whole-prostate cryoablation and ADT and received pembrolizumab.[10] This study found that the treatment had a manageable safety profile, although prolonged disease control beyond testosterone recovery was rare.[10]

The randomized, placebo-controlled, double-blind, phase III KEYNOTE-991 study evaluated the efficacy and safety of pembrolizumab versus placebo in combination with enzalutamide and ADT in participants with NHA-naive mHSPC. We present the results of the first prespecified interim analysis.

PATIENTS AND METHODS

Study design and participants

The KEYNOTE-991 study (ClinicalTrials.gov identifier: NCT04191096) was conducted at 226 global sites. Eligible participants were males aged $\geq$18 years with histologically or cytologically confirmed prostate adenocarcinoma (without small-cell histology) and two or more bone metastases and/or visceral disease, as assessed by the investigator and verified by blinded independent central review (BICR). BICR of metastatic status was included because in the ARCHES study, retrospective assessment by BICR revealed that ~6.9% of enrolled participants had no confirmed metastases at screening.[11] Participants must have maintained either continuous ADT or had a history of bilateral orchiectomy and had an Eastern Cooperative Oncology Group performance status score of 0 or 1. Additionally, a newly obtained ($\leq$12 months before screening) core or excisional biopsy sample from soft tissue not previously irradiated must have been provided (a bone biopsy sample was acceptable for participants with bone-predominant disease). Before randomization, participants could undergo $\leq$3 months of ADT, six or fewer cycles of docetaxel with ADT (completed $\leq$2 months before randomization), and one course of palliative radiation or surgical therapy (or, for participants with low-volume disease, one course of definitive radiotherapy completed $\geq$4 weeks before randomization) for metastatic prostate cancer.

Key exclusion criteria included prior therapy with an NHA or an immune checkpoint inhibitor; prior ADT as neoadjuvant/adjuvant therapy for nonmetastatic prostate cancer for >39 months or $\leq$9 months before randomization, or with evidence of disease progression while receiving ADT; and metastatic disease restricted to the lymph nodes. Participants were also excluded if they had a superscan appearance at screening caused by diffuse skeletal involvement of the tumor resulting in individual bone lesions being indistinguishable on the scan. In this case, additional bone metastases would not be evaluable in the future. Additional information can be found in the KEYNOTE-991 study design publication[12] and in the protocol (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.05.009).

The protocol and all amendments were approved by the appropriate ethics committees at each participating institution. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent. The study was overseen by an executive oversight committee. Efficacy and safety were assessed at the prespecified first interim analysis by an independent, external data monitoring committee.

Study procedures

Participants were randomly assigned (1 : 1) to receive pembrolizumab 200 mg intravenously once every 3 weeks for $\leq$35 cycles (~2 years) or saline placebo intravenously for $\leq$35 cycles in combination with continuous enzalutamide 160 mg orally once daily starting on day 1 of cycle 1, and ADT in accordance with local product labeling (or bilateral orchiectomy). The randomized allocation schedule was generated by the Clinical Biostatistics Department of the sponsor and implemented by a trial vendor using central interactive response technology. Blinding was conducted using in-house blinding procedures. Enzalutamide treatment could continue if participants discontinued pembrolizumab or placebo for reasons other than disease progression.

Randomization was stratified by prior docetaxel therapy (yes versus no) and the presence of high-volume disease (yes versus no). High-volume disease was defined as per the CHAARTED criteria[13] as the presence of metastases involving the viscera, or, in the absence of visceral lesions, four or more bone lesions, one or more of which must be in

a bony structure beyond the vertebral column and pelvic bone.

Endpoints and assessments

The dual primary endpoints were radiographic progression-free survival [rPFS; time from randomization to radiographic progression as determined per Prostate Cancer Clinical Trials Working Group (PCWG)-modified RECIST version 1.1 by BICR, or death from any cause] and overall survival (OS; time from randomization to death from any cause). Key secondary efficacy endpoints were time to first subsequent anticancer therapy (TFST; defined as time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurred first) and time to first symptomatic skeletal-related event (TTSSRE; defined as time from randomization to the first use of external beam radiotherapy to prevent or relieve skeletal symptoms, occurrence of new symptomatic pathological bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention, whichever occurred first).

Additional secondary endpoints included objective response rate (ORR) as per PCWG-modified RECIST v1.1 by BICR, prostate-specific antigen (PSA) response rate ($\geq$50% reduction from baseline assessed twice, $\geq$3 weeks apart), and time to PSA progression (defined as time from randomization to increase of $\geq$25% and 2 ng/ml above nadir or baseline, whichever was lower).

Patient-reported outcome (PRO) endpoints included time to pain progression [defined as time from randomization to the earliest date of pain progression based on the Brief Pain Inventory—Short Form (BPI-SF) item 3 'worst pain in 24 hours' and opiate use][14] and least squares mean (LSM) change from baseline to week 69 in BPI-SF (worst pain, pain severity, and pain interference) scores and Functional Assessment of Cancer Therapy—Prostate (FACT-P)[15,16] total and subscale scores. For the LSM change from baseline analyses, week 69 was selected as the latest time point where the completion and compliance rates for each PRO instrument were >60% and >80% as per protocol, respectively, based on blinded data review before the data cut-off date for PRO assessments. Efficacy, safety, and PRO assessment methods are provided in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2025.05.009.

Statistical analysis

Efficacy analyses were carried out in the intention-to-treat (ITT) population, defined as all randomly assigned participants. Safety analyses were carried out in the as-treated population, defined as all randomly assigned participants who received one or more doses of study treatment. Analyses of PROs were carried out in the PRO full-analysis set, defined as all randomly assigned participants who had one or more PRO assessments available and had received one or more doses of study treatment.

For rPFS, OS, TFST, TTSSRE, time to PSA progression, and time to pain progression, hazard ratios (HRs) were estimated using a stratified Cox regression model, and medians and event rates over time were estimated using the Kaplan—Meier method. Between-arm differences in rPFS were analyzed using a stratified log-rank test. Incidence of adverse events (AEs) was summarized descriptively. Prespecified subgroup analyses were based on an unstratified Cox regression model with treatment as a covariate.

The planned sample size was 1232 participants. A power analysis estimated that 652 rPFS events at the primary rPFS analysis would give 80% power to detect superiority of pembrolizumab plus enzalutamide and ADT over placebo plus enzalutamide and ADT at an overall one-sided α level of 2.5% (HR 0.80), and 600 OS events at the final analysis would give 77% power at an overall one-sided α level of $\sim$2.5%. Five interim analyses were planned. The first prespecified interim analysis was planned to occur 32 months after the first participant was randomly assigned. According to the data analysis plan, OS would only be formally evaluated if the rPFS null hypothesis was rejected. Additional details are listed in the statistical analysis plan and study protocol (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.05.009).

RESULTS

Participants

Between 2 March 2020 and 9 August 2021, 1251 participants were randomly assigned to receive pembrolizumab plus enzalutamide and ADT (n = 626) or placebo plus enzalutamide and ADT (n = 625; ITT population; Figure 1). Baseline characteristics were well balanced between treatment arms (Table 1). Docetaxel had been previously administered to 64 participants (10.2%) in the pembrolizumab plus enzalutamide and ADT arm and 61 participants (9.8%) in the placebo plus enzalutamide and ADT arm.

At the first interim analysis, median time from randomization to data cut-off date (31 October 2022) was 21.1 months (range 14.8-32.0 months). Overall, 404 (64.5%) and 424 (67.8%) participants completed the study regimen in the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm, respectively. The study regimen was discontinued by 221 (35.4%) and 201 (32.2%) participants in the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm, respectively, most commonly due to radiographic disease progression (15.8% and 19.0%, respectively) or AEs (12.2% and 5.1%, respectively).

Efficacy

Median rPFS was not reached in either arm [HR 1.20, 95% confidence interval (CI) 0.96-1.49, P = 0.9467; Figure 2A]. Prespecified subgroup analyses of rPFS were generally consistent with the primary rPFS analysis (Figure 3A). No favorable trend in OS was observed between treatment arms (median OS not reached in either arm; HR 1.16, 95% CI

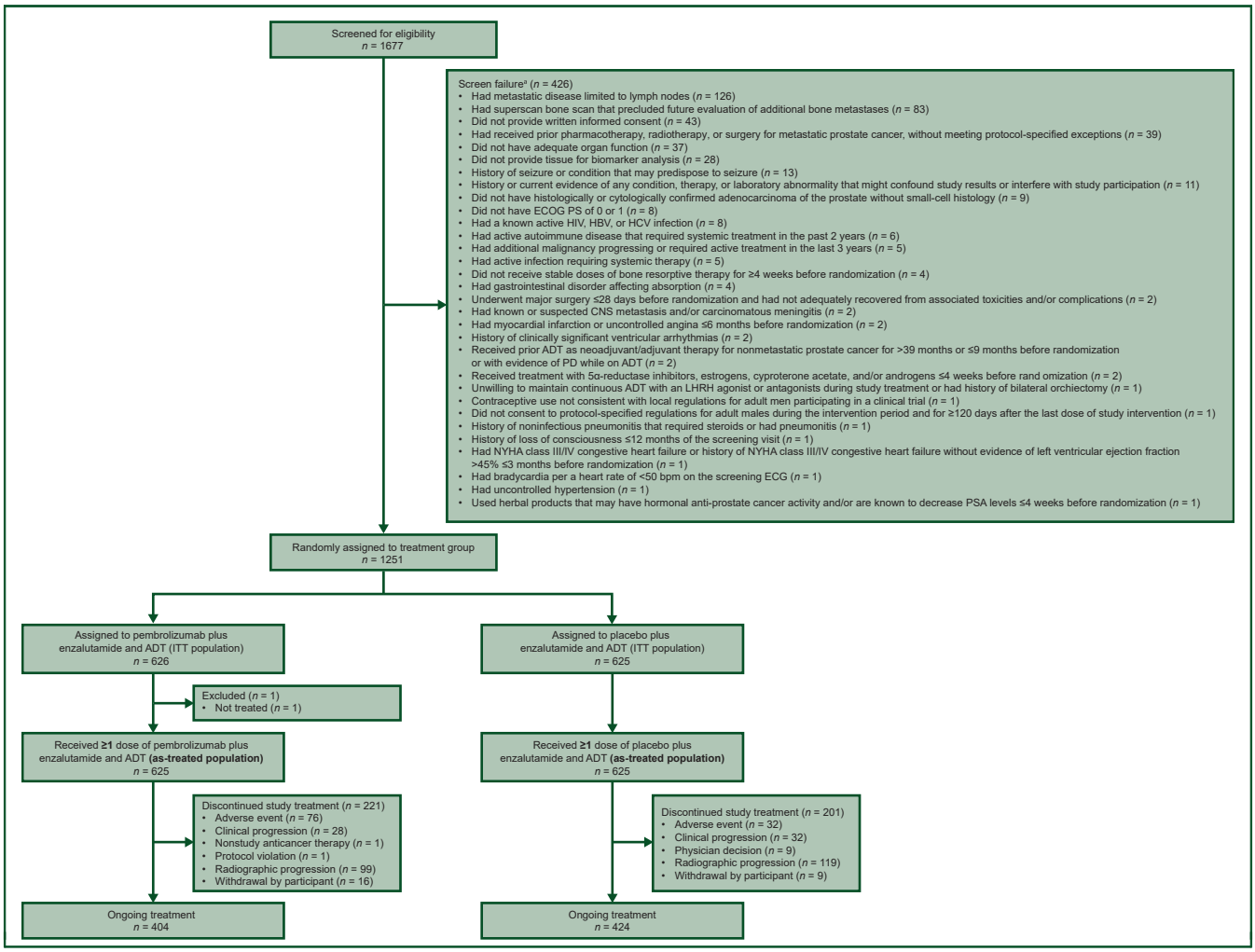


Figure 1. CONSORT diagram.
ADT, androgen deprivation therapy; bpm, beats per minute; CNS, central nervous system; CONSORT, Consolidated Standards of Reporting Trials; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ITT, intention-to-treat; LHRH, luteinizing hormone-releasing hormone; NYHA, New York Heart Association; PD, progressive disease; PSA, prostate-specific antigen.
[a]Patients could have more than one reason for screen failure.

0.88-1.53; not formally statistically tested as per the multiplicity strategy; Figure 2B). Prespecified subgroup analyses of OS were generally consistent with the overall OS analysis (Figure 3B).

TFST and TTSSRE showed no favorable trend for pembrolizumab plus enzalutamide and ADT versus placebo plus enzalutamide and ADT (TFST: median not reached; HR 1.24, 95% CI 1.01-1.54; TTSSRE: median not reached; HR 0.89, 95% CI 0.61-1.30; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.05.009). ORR in participants with RECIST-measurable disease at baseline [65.7% (163/248) versus 71.8% (176/245); Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.05.009] and PSA response rate in participants with baseline PSA measurements [90.3% (559/619) versus 93.0% (574/617)] were similar between the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm. Median time to PSA progression was not reached in both treatment arms (HR 0.92, 95% CI 0.69-1.23; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.05.009).

Safety

Overall, 625 participants in each arm received one or more doses of study treatment. Median (range) duration of therapy was 17.6 months (0.03-31.6 months) in the pembrolizumab plus enzalutamide and ADT arm and 18.4 months (0.4-30.5 months) in the placebo plus enzalutamide and ADT arm.

Most participants experienced one or more AEs of any cause [pembrolizumab plus enzalutamide and ADT, $n = 618$ (98.9%); placebo plus enzalutamide and ADT, $n = 595$ (95.2%); Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.05.009]. A higher frequency of grade ≥ 3 [$n = 387$ (61.9%) versus $n = 238$ (38.1%)] and serious AEs [SAEs; $n = 252$ (40.3%) versus $n = 145$

Table 1. Baseline demographics and characteristics in the intention-to-treat population

	Pembrolizumab plus enzalutamide and ADT (n = 626)	Placebo plus enzalutamide and ADT (n = 625)
Age, median (range), years	68 (43-91)	68 (37-90)
≥65, *n* (%)	406 (64.9)	416 (66.6)
Race,[a] *n* (%)		
American Indian or Alaska Native	19 (3.0)	13 (2.1)
Asian	99 (15.8)	118 (18.9)
Black or African American	17 (2.7)	14 (2.2)
Multiple	39 (6.2)	37 (5.9)
White	447 (71.4)	440 (70.4)
Ethnicity, *n* (%)		
Hispanic or Latino	119 (19.0)	112 (17.9)
Geographic region, *n* (%)		
North America	76 (12.1)	86 (13.8)
Western Europe	255 (40.7)	245 (39.2)
Rest of the world	295 (47.1)	294 (47.0)
ECOG performance status score, *n* (%)		
0	416 (66.5)	444 (71.0)
1	210 (33.5)	181 (29.0)
Gleason score, *n* (%)		
≤7	148 (23.6)	124 (19.8)
≥8	458 (73.2)	487 (77.9)
Unknown	20 (3.2)	14 (2.2)
Type of metastases,[b] *n* (%)		
Bone only	319 (51.0)	322 (51.5)
Soft tissue only	22 (3.5)	16 (2.6)
Bone and soft tissue	285 (45.5)	287 (45.9)
Presence of visceral metastases, *n* (%)	127 (20.3)	119 (19.0)
Prior docetaxel, *n* (%)	64 (10.2)	61 (9.8)
Duration of prior docetaxel, median (range), months	3.5 (0.0-5.7)	3.5 (0.0-4.6)
High-volume disease,[c] *n* (%)	392 (62.6)	398 (63.7)
Prior local therapy, *n* (%)		
Radiation only	81 (12.9)	63 (10.1)
Radical prostatectomy only	14 (2.2)	20 (3.2)
Radiation and radical prostatectomy	31 (5.0)	33 (5.3)
Other surgeries	500 (79.9)	509 (81.4)
Duration of prior ADT, median (range), months	1.8 (0.0-40.0)	1.6 (0.0-38.3)
PD-L1 status,[d] *n* (%)		
Positive	238 (38.0)	252 (40.3)
Negative	377 (60.2)	363 (58.1)
Not evaluable/unknown	11 (1.8)	10 (1.6)
Baseline PSA, ng/ml, median (range)	6.0 (0.1-4193.0)	6.7 (0.1-5000.0)
RECIST-measurable disease,[e] *n* (%)	248 (39.6)	245 (39.2)

The intention-to-treat population includes all randomly assigned participants.
ADT, androgen deprivation therapy; BICR, blinded independent central review; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PSA, prostate-specific antigen.
[a]Participant numbers for the Native Hawaiian or Other Pacific Islander category were very low, the reporting of which would lead to a risk of identification.
[b]Lesion location determined by BICR.
[c]High-volume disease defined as the presence of visceral metastases or four or more bone lesions with one or more beyond the vertebral bodies and pelvis.
[d]Assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technlogies, Carpinteria, CA). CPS was the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. PD-L1 positive was defined as having CPS ≥1; PD-L1 negative was defined as having CPS <1.
[e]Measurable disease determined by BICR.

(23.2%)] occurred in the pembrolizumab plus enzalutamide and ADT arm versus the placebo plus enzalutamide and ADT arm.

Fatigue, arthralgia, and rash were the most common AEs in the pembrolizumab plus enzalutamide and ADT arm (≥10% of participants; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.05.009). The incidence of rash was notably higher in the pembrolizumab plus enzalutamide and ADT arm versus the placebo plus enzalutamide and ADT arm [n = 157 (25.1%) versus n = 58 (9.3%)]. Maculopapular rash and pruritus were also reported with a higher frequency in the pembrolizumab plus enzalutamide and ADT arm versus the placebo plus enzalutamide and ADT arm [n = 65 (10.4%) versus n = 15 (2.4%) and n = 110 (17.6%) versus n = 55 (8.8%), respectively].

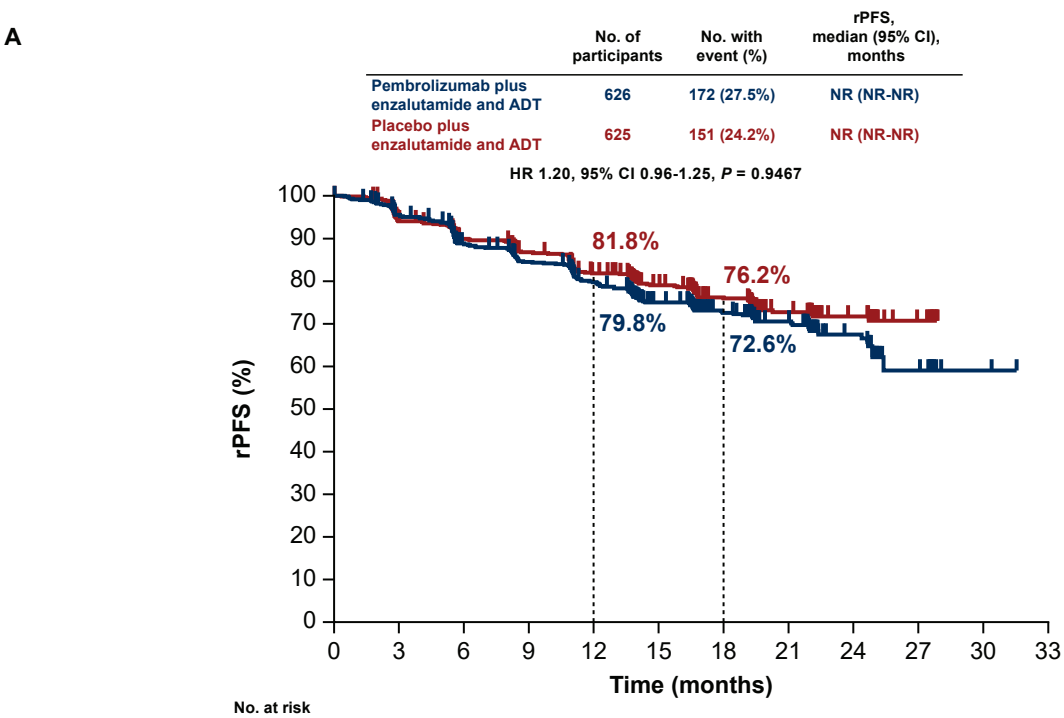
SAEs occurring with a frequency of >1.0% in the pembrolizumab plus enzalutamide and ADT arm included urinary tract infection [n = 11 (1.8%)], rash [n = 10 (1.6%)], maculopapular rash [n = 10 (1.6%)], pneumonia [n = 9 (1.4%)], colitis [n = 7 (1.1%)], myocardial infarction [n = 7 (1.1%)], and pneumonitis [n = 7 (1.1%); Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.05.009].

Overall, 209 (33.4%) and 51 (8.2%) participants in the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm, respectively, discontinued treatment due to AEs (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.05.009). AEs leading to treatment discontinuation in >1.0% of participants who received pembrolizumab plus enzalutamide and ADT were pneumonitis [n = 14 (2.2%)], alanine aminotransferase level increased [n = 13 (2.1%)], rash [n = 12 (1.9%)], diarrhea [n = 11 (1.8%)], aspartate aminotransferase level increased [n = 9 (1.4%)], colitis [n = 7 (1.1%)], and immune-mediated hepatitis [n = 7 (1.1%)].

Overall, 550 (88.0%) and 419 (67.0%) participants in the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm, respectively, experienced one or more treatment-related AEs, with 261 (41.8%) and 87 (13.9%) participants, respectively, experiencing a treatment-related AE of grade ≥3 (Table 2).

AEs leading to death were reported in 33 (5.3%) and 16 (2.6%) participants in the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm, respectively (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.05.009). Six participants (1.0%) in the pembrolizumab plus enzalutamide and ADT arm and one participant (0.2%) in the placebo plus enzalutamide and ADT arm died from a treatment-related AE (Table 2). The treatment-related AE leading to death in the pembrolizumab plus enzalutamide and ADT arm was autoimmune myositis, cardiac failure, hypoglycemia, immune-mediated lung disease, interstitial lung disease, pneumonitis, and septic shock [each, n = 1 (0.2%); Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.05.009]. The treatment-related AE that led to death in the placebo plus enzalutamide and ADT arm was cardiac arrest [n = 1 (0.2%)].

Immune-mediated AEs and infusion reactions were reported in 270 (43.2%) and 47 (7.5%) participants in the pembrolizumab plus enzalutamide and ADT arm and the



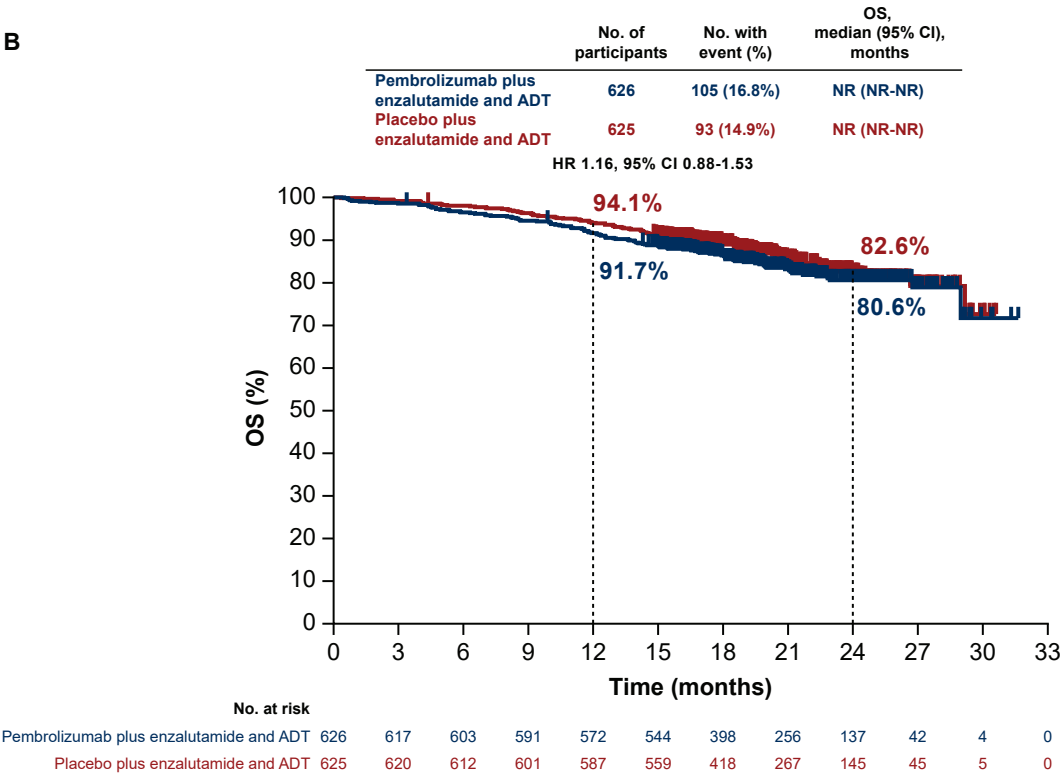
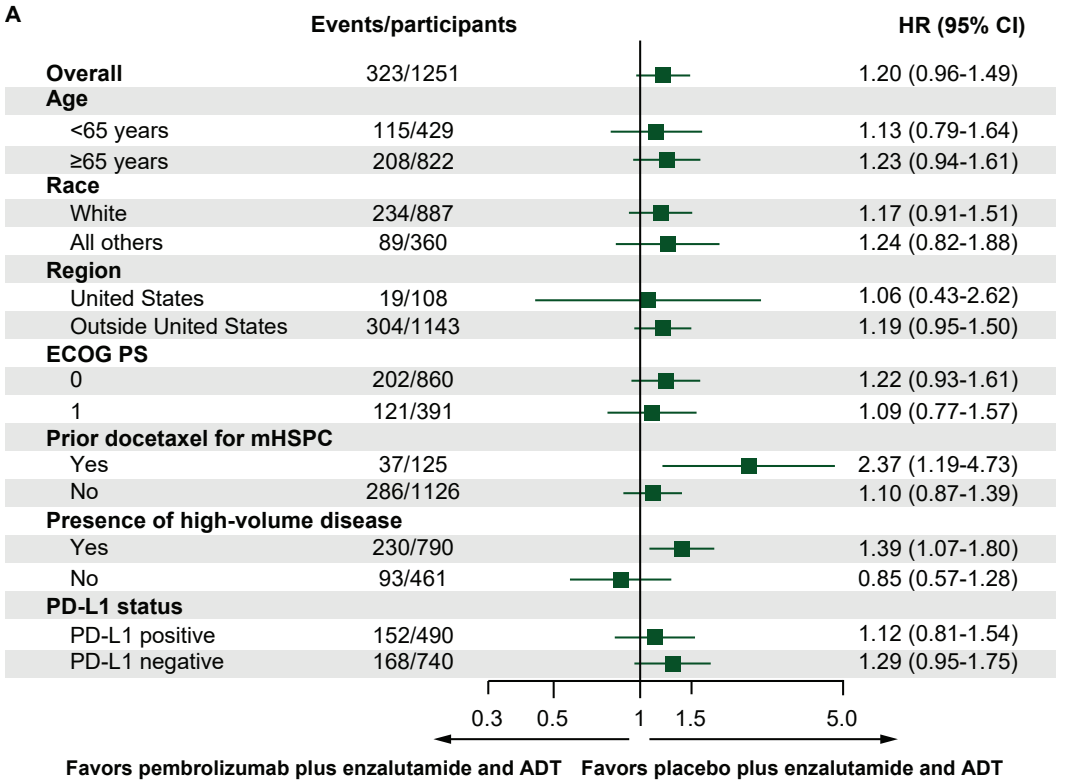


Figure 2. rPFS and OS in the intention-to-treat population.[a] Kaplan-Meier estimates of (A) rPFS as per PCWG-modified RECIST v1.1 by BICR and (B) OS.[b]
ADT, androgen deprivation therapy; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PCWG, Prostate Cancer Clinical Trials Working Group; rPFS, radiographic progression-free survival.
[a]The intention-to-treat population includes all randomly assigned participants.
[b]OS was not formally statistically tested as per the multiplicity strategy.

https://doi.org/10.1016/j.annonc.2025.05.008



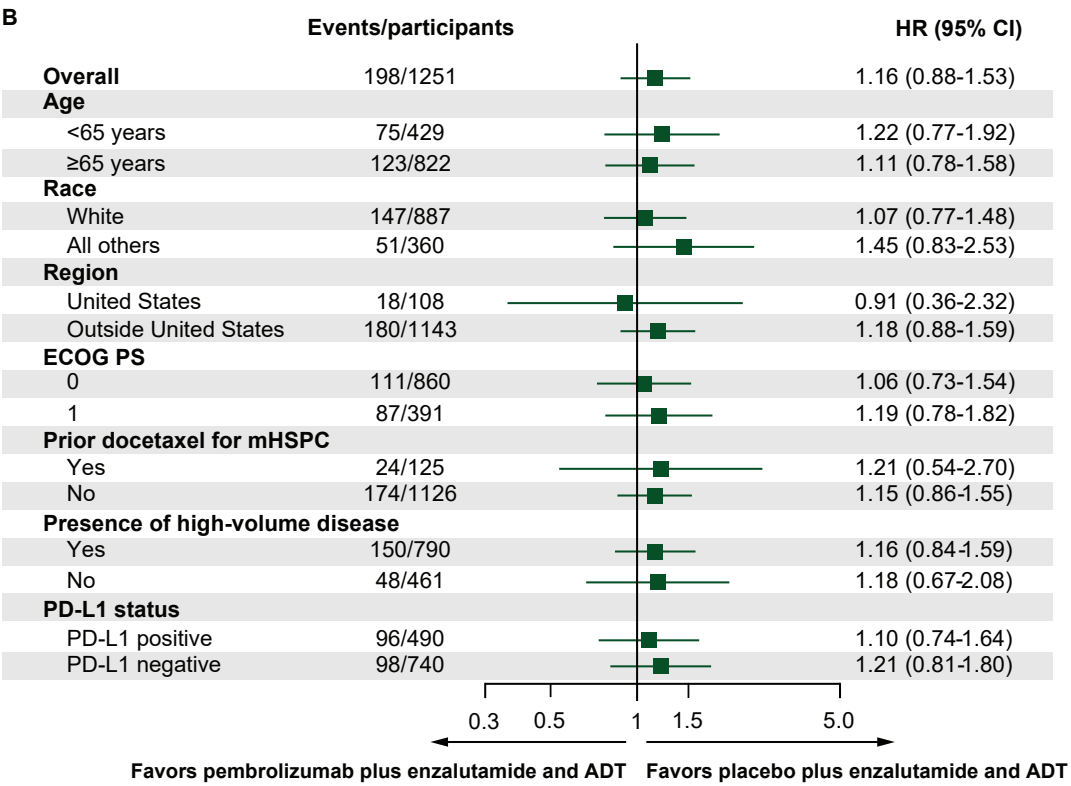


Figure 3. Subgroup analysis of rPFS and OS in the intention-to-treat population.[a,b] (A) rPFS as per PCWG-modified RECIST v1.1 by BICR and (B) OS.
ADT, androgen deprivation therapy; BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival; PCWG, Prostate Cancer Clinical Trials Working Group; PD-L1, programmed death-ligand 1; rPFS, radiographic progression-free survival.
[a]Subgroup analysis was not carried out for subgroup variables with <10% of the total intention-to-treat population, except for region and prior docetaxel for mHSPC.
[b]The intention-to-treat population includes all randomly assigned participants.

Table 2. Summary of treatment-related adverse events in the as-treated population[a]

	Pembrolizumab plus enzalutamide and ADT (n = 625)		Placebo plus enzalutamide and ADT (n = 625)	
Any, n (%)	550 (88.0)		419 (67.0)	
Grade 3-5	261 (41.8)		87 (13.9)	
Leading to treatment discontinuation	171 (27.4)		27 (4.3)	
Serious	114 (18.2)		18 (2.9)	
Serious and led to treatment discontinuation	80 (12.3)		9 (1.4)	
Leading to death	6 (1.0)		1 (0.2)	
Treatment-related adverse event with incidence ≥5%, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Fatigue	139 (22.2)	29 (4.6)	124 (19.8)	16 (2.6)
Rash	125 (20.0)	43 (6.9)	32 (5.1)	3 (0.5)
Pruritus	75 (12.0)	1 (0.2)	30 (4.8)	0
Hypothyroidism	70 (11.2)	0	20 (3.2)	0
Arthralgia	68 (10.9)	3 (0.5)	34 (5.4)	2 (0.3)
Diarrhea	67 (10.7)	10 (1.6)	26 (4.2)	1 (0.2)
Asthenia	60 (9.6)	6 (1.0)	33 (5.3)	6 (1.0)
Alanine aminotransferase increased	59 (9.4)	11 (1.8)	24 (3.8)	4 (0.6)
Hot flush	59 (9.4)	2 (0.3)	86 (13.8)	1 (0.2)
Maculopapular rash	58 (9.3)	27 (4.3)	10 (1.6)	1 (0.2)
Aspartate aminotransferase increased	52 (8.3)	9 (1.4)	22 (3.5)	2 (0.3)
Nausea	51 (8.2)	2 (0.3)	28 (4.5)	1 (0.2)
Hypertension	48 (7.7)	22 (3.5)	64 (10.2)	27 (4.3)
Decreased appetite	38 (6.1)	3 (0.5)	12 (1.9)	0

Each participant is counted once for each applicable adverse event by maximum toxicity grade.
ADT, androgen deprivation therapy.
[a]The as-treated population includes all randomly assigned participants who received one or more doses of study treatment.

placebo plus enzalutamide and ADT arm, respectively; grade ≥3 events were reported in 134 (21.4%) and 8 (1.3%) participants, respectively (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.05.009). Overall, four participants (0.6%) who received pembrolizumab plus enzalutamide and ADT died due to an immune-mediated AE or infusion reaction. High-dose systemic corticosteroids (≥40 mg/day prednisone or equivalent) were administered to treat immune-mediated AEs and infusion reactions in 87 participants (32.2%) in the pembrolizumab plus enzalutamide and ADT arm and 6 participants (12.8%) in the placebo plus enzalutamide and ADT arm. Severe skin reactions were reported in 106 participants (17.0%) in the pembrolizumab plus enzalutamide and ADT arm and in 4 participants (0.6%) in the placebo plus enzalutamide and ADT arm. High-dose systemic corticosteroids were administered for severe skin reactions in 45 participants (42.5%) in the pembrolizumab plus enzalutamide and ADT arm and 1 participant (25.0%) in the placebo plus enzalutamide and ADT arm.

Patient-reported outcomes

Median time to pain progression was not reached in either the pembrolizumab plus enzalutamide and ADT arm or the placebo plus enzalutamide and ADT arm (HR 1.15, 95% CI 0.95-1.39; Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.05.009).

Completion rates for the BPI-SF and FACT-P questionnaires to week 69 were >60% (Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2025.05.009). Mean FACT-P total score, functional well-being (FWB) subscale score, and trial outcome index (TOI) score declined to a greater extent from baseline to week 69 for participants who received pembrolizumab plus enzalutamide and ADT versus placebo plus enzalutamide and ADT [LSM treatment difference (95% CI): FACT-P −2.34 (−4.63 to −0.05); FWB −0.72 (−1.40 to −0.04); TOI −2.17 (−3.90 to −0.44); Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.05.009]. All other mean PRO scores changed to a similar extent in both treatment arms (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.05.009). The proportion of participants with a best PRO response of improved, stable, or deteriorated was similar between the pembrolizumab plus enzalutamide and ADT arm and the placebo plus enzalutamide and ADT arm for all FACT-P subscales and the FACT-P total score (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2025.05.009).

DISCUSSION

In the phase III KEYNOTE-991 study of pembrolizumab versus placebo in combination with enzalutamide and ADT for participants with NHA-naive mHSPC, the primary efficacy endpoint of superior rPFS was not met at the first interim analysis, and the study was terminated due to futility. Other efficacy outcomes, including OS and ORR, also showed no favorable trend for the pembrolizumab plus enzalutamide and ADT arm versus the placebo plus enzalutamide and ADT arm. The higher incidence of AEs (including high-grade AEs and SAEs) as well the higher rate of discontinuation due to AEs in the pembrolizumab plus enzalutamide and ADT arm versus the placebo plus enzalutamide and ADT arm may have influenced the results. PROs were similar between treatment arms.

Cohort C of the phase Ib/II KEYNOTE-365 study and cohorts 4 and 5 of the phase II KEYNOTE-199 study reported a promising ORR for participants with mCRPC treated with pembrolizumab and enzalutamide (11% and 12.3%, respectively).[8,9] Similarly, the phase II CheckMate 9KD study reported an ORR of 11.1% for the combination of the PD-1 inhibitor nivolumab and enzalutamide in mCRPC (OS and rPFS results not yet available).[17] However, other phase III clinical studies did not show a benefit with programmed cell death protein/ligand 1 (PD-[L]1) inhibitors and enzalutamide versus enzalutamide alone in the mCRPC setting.[18,19] KEYNOTE-641 did not meet the dual primary endpoints of rPFS (HR 0.98, 95% CI 0.84-1.14, $P = 0.41$) and OS (HR 1.04, 95% CI 0.88-1.22, $P = 0.66$) at the first interim analysis of the efficacy of pembrolizumab and enzalutamide, and the study was stopped for futility.[19] Similarly, the phase III IMbassador250 study of participants with mCRPC did not

find an OS advantage with the addition of atezolizumab to enzalutamide (HR 1.12, 95% CI 0.91-1.37, $P = 0.28$).[18] These results are in alignment with the results reported here for mHSPC.

A higher frequency of rash was reported in participants who received pembrolizumab plus enzalutamide and ADT versus placebo plus enzalutamide and ADT, which was higher than expected for either pembrolizumab or enzalutamide alone.[20-22] A high incidence of rash is consistent with prior studies combining pembrolizumab and enzalutamide in prostate cancer.[8,9] In cohorts 4 and 5 of the phase II single-arm KEYNOTE-199 study of pembrolizumab with enzalutamide for mCRPC progressing on enzalutamide, treatment-related rash and treatment-related maculopapular rash were reported in 14.3% and 10.3% of participants, respectively.[8] In cohort C of the phase Ib/II KEYNOTE-365 study (pembrolizumab with enzalutamide for chemotherapy-naive mCRPC progressing on first-line abiraterone acetate), treatment-related rash and treatment-related maculopapular rash were reported in 22% and 13% of participants, respectively, and treatment-related rash led to discontinuation in 2.0% of participants.[9] Similarly, the IMbassador250 study reported a higher frequency of rash in the atezolizumab plus enzalutamide (25.9%) versus the enzalutamide-only arm (6.6%).[18] The phase II CheckMate 9KD study also reported a high frequency of immune-mediated rash in participants with mCRPC receiving nivolumab with enzalutamide (20.4%).[17] These results are consistent with an increased likelihood of rash for the combination of an anti-PD-(L)1 pathway inhibitor with enzalutamide versus either agent alone.

Notably, the incidence of any-grade immune-mediated pneumonitis in the pembrolizumab plus enzalutamide and ADT arm (6.4%) is higher than that previously reported for pembrolizumab plus enzalutamide in phase II studies of participants with mCRPC (KEYNOTE-199 cohorts 4 and 5: 2.4%; KEYNOTE-365 cohort C: 1.0%).[9,23] The higher incidence of immune-related pneumonitis may be due to the longer median duration of treatment in KEYNOTE-991 (median 17.6 months) compared with those of KEYNOTE-199 (cohort 4: median 3.5 months; cohort 5: median 4.6 months) and KEYNOTE-365 cohort C (median 6.2 months).[9,23]

It remains unclear whether PD-1 pathway inhibitors as monotherapy or in combination with other anticancer therapies have a role in the treatment of molecularly unselected patients with prostate cancer. Phase III studies investigating pembrolizumab in combination with olaparib (KEYLYNK-010) or docetaxel (KEYNOTE-921) for mCRPC showed no improvement in rPFS (HR 1.02, 95% CI 0.82-1.25, $P = 0.55$ and HR 0.85, 95% CI 0.71-1.01, $P = 0.03$, respectively) or OS (HR 0.94, 95% CI 0.77-1.14, $P = 0.26$ and HR 0.92, 95% CI 0.78-1.09, $P = 0.17$, respectively) versus abiraterone or enzalutamide, or versus placebo plus enzalutamide and ADT with docetaxel, respectively.[24,25] However, it is possible that specific prostate cancer subtypes may be susceptible to PD-1 pathway inhibition. Recently, studies have demonstrated the efficacy of dual immune checkpoint blockade in selected populations of participants with mCRPC based on immunogenic features.[26,27] In the phase II INSPIRE study of nivolumab plus ipilimumab followed by nivolumab maintenance in molecularly selected participants with mCRPC, improvement in the primary endpoint of disease control rate beyond 6 months was observed in 38% of all participants, with exceptionally high antitumor activity observed in the subset of participants with deficient DNA mismatch repair (disease control rate beyond 6 months, 81%).[27] In the phase II NEPTUNES study of biomarker-selected participants with mCRPC, up to 44% of participants with exclusively high tumor-infiltrating lymphocytes had a response to nivolumab plus ipilimumab, indicating that inflammatory infiltrate is a promising predictive biomarker in mCRPC.[26] Results from the phase II CheckMate 650 study of unselected participants with chemotherapy-naive or chemotherapy-experienced mCRPC show the efficacy of nivolumab plus ipilimumab in this setting, with preliminary exploratory data indicating enriched clinical activity in the subset of participants with relatively high tumor mutational burden.[28,29] Other studies are under way to investigate PD-1 pathway inhibitor monotherapy or combination therapy in participants with tumors predicted to be more highly immunogenic based on their molecular or histologic characteristics (e.g. CHOMP and NCT04126070), including DNA damage repair defects and *CDK12* mutations.[30,31] Pembrolizumab combined with platinum-based chemotherapy is being investigated as a therapy for treatment-emergent neuroendocrine mCRPC in cohort I of the phase Ib/II KEYNOTE-365 study.[32]

Strengths of this KEYNOTE-991 study include its robust, randomized, double-blind, and active-controlled design. However, early termination of the study meant that long-term follow-up was limited and that median values for many endpoints were not reached. The power to detect treatment-related differences was therefore low at this first interim analysis. Patients with poor performance status or node-only metastases were excluded from the study; therefore, the efficacy and safety profiles of pembrolizumab in combination with enzalutamide are unclear in these patients. Additional limitations of this study include a lack of biomarker analysis to elucidate molecular determinants of response to treatment and the low proportion of particular racial subgroups in this study (e.g. Pacific Islander), which makes extrapolating results to these populations difficult.

The results of this phase III KEYNOTE-991 study do not support the addition of pembrolizumab to enzalutamide and ADT for the treatment of mHSPC due to a lack of superiority and increased frequency of high-grade AEs and SAEs versus placebo plus enzalutamide and ADT. In particular, rash was reported more frequently in the pembrolizumab plus enzalutamide and ADT arm versus the placebo plus enzalutamide and ADT arm. These results concur with recent results in mCRPC studies and highlight the need for further work to identify the role of immune checkpoint inhibitors in the treatment of advanced prostate cancer.

ACKNOWLEDGEMENTS

The authors thank the participants, their families, and caregivers for their involvement in this trial and all investigators and site personnel. Astellas Pharma Inc. provided the enzalutamide for this study. The authors acknowledge Helen Wu, PhD, of Merck & Co., Inc., Rahway, NJ, USA, for valuable statistical input. Medical writing support was provided by Obinna T. Ezeokoli, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

FUNDING

This work was supported by Merck Sharp & Dohme LLC (no grant number), a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

DISCLOSURE

CG reports funding and medical writing support for the present work from MSD; research grants or contracts from Astellas Pharma, AstraZeneca, Bayer, Janssen, MSD, and Steba Biotech; consulting fees from Astellas Pharma, AstraZeneca, Bayer, Janssen, and MSD; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, Astellas Pharma, AstraZeneca, Bayer, Eli Lilly, GlaxoSmithKline, Ipsen, Janssen, MSD, and Pfizer; support for attending meetings and/or travel from Astellas Pharma, Bayer, Ipsen, and Janssen; and serves as a treasurer for the Urological Research Society and as editor-in-chief for the *European Urology Focus* journal outside the submitted work. MÖ reports consulting fees for participation on an advisory board for MSD and Sanofi; consulting fees for participation on a steering committee for AstraZeneca; payment for expert testimony from MSD; and support for travel from Regeneron outside the submitted work. AP reports receiving consulting fees from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Janssen-Cilag, Merck Serono, MSD Oncology, Novartis, Pfizer, and Takeda; support for attending meetings and/or travel from Astellas Pharma, Bristol Myers Squibb, MSD, and Pfizer; and honoraria from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Exelixis, Janssen Oncology, Medison, Merck Serono, MSD, and Roche outside the submitted work. MANS reports consulting fees from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, and Takeda; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Gilead, Janssen, MSD, Novartis, Pfizer, Roche, and Takeda outside the submitted work. JCG reports grants or contracts from Cancer Australia and Medical Research Future Fund Australia; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Bayer, Eisai, GlaxoSmithKline, and MSD; support for attending meetings and/or travel from Bayer Australia; and participation on a data safety monitoring board or advisory board for Eisai, GlaxoSmithKline, and MSD outside the submitted work. GJ reports support for the present manuscript from MSD; consulting fees from AstraZeneca, KDx, MSD, Photocure, and Specialty Networks; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Bayer, MSD, and Photocure; support for attending meetings and/or travel from Specialty Networks; and participation on a data safety monitoring board or advisory board for AstraZeneca, Janssen, MSD, and UroGen outside the submitted work. SSB reports clinical research grants or contracts from Astellas Pharma, AstraZeneca, Bayer, Janssen, MSD, and Pfizer; consulting fees from Astellas Pharma, AstraZeneca, Bayer, and Janssen; honoraria for lecture and/or moderation from Astellas Pharma, AstraZeneca, Bayer, and Janssen; and is the founder and a stockholder of Procagen outside the submitted work. CK reports support for the present manuscript from MSD; clinical research grant or contracts from Astellas Pharma and Janssen; consulting fees from Astellas Pharma and Janssen; payment or honoraria for lectures, presentations, speakers bureaus, and manuscript writing or educational events from Astellas Pharma and Janssen; support for attending meetings and/or travel from Astellas Pharma and Janssen; participation on a data safety monitoring board or advisory board for Astellas Pharma and Janssen; and holds a leadership or fiduciary role in the Korean Urological Oncology Society outside the submitted work. RMK reports support for the present work from MSD; educational grants and/or clinical research grants from AbbVie, Amgen, Astellas Pharma, Bayer, Bristol Myers Squibb, Eli Lilly, Ipsen, Janssen, Merck Serono, MSD, Novartis, Pfizer, Roche, Sanofi, and Tecnofarma; consulting fees from Amgen, Astellas Pharma, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, and Tecnofarma; payment or honoraria for lectures, presentations, speakers bureaus, and manuscript writing or educational events from Amgen, Astellas Pharma, Bayer, Bristol Myers Squibb, Eli Lilly, Ipsen, Janssen, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, and Tecnofarma; support for attending meetings and/or travel from Amgen, Ipsen, MSD, and Pfizer; participation on advisory board for Amgen, Astellas Pharma, Bayer, Bristol Myers Squibb, Ipsen, Janssen, MSD, Novartis, Pfizer, and Tecnofarma; and board membership of Asociación Colombiana de Hematología y Oncología outside the submitted work. JCVL reports writing support for the present manuscript from MSD; research funding from AbbVie, Amgen, GlaxoSmithKline, MSD, Novartis, Regeneron, Roche, and Seagen; grant or contract for advisory and/or speaker role from Novartis and Roche; consulting fees for advisory role from AstraZeneca and MSD; payment or honoraria for speakers bureaus from MSD; and support for attending World Conference on Lung Cancer from Janssen outside the submitted work. JFEP reports for the present manuscript from MSD; clinical research grants from AstraZeneca, Bristol Myers Squibb, and MSD; payment or honoraria for lectures, presentations, speakers bureaus, and manuscript writing or

educational events from Asofarma; support for attending meetings and/or travel from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Janssen, MSD, and Roche; and membership of the board of Sociedad Mexicana de Oncología (SMEO) outside the submitted work. UDG reports consulting fees paid to him from Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Ipsen, Janssen, Merck KGaA, MSD, Novartis, and Pfizer; support for attending meetings and/or travel from AstraZeneca, Ipsen, and Pfizer; and other financial or nonfinancial interests to his institution from AstraZeneca, Roche, and Sanofi outside the submitted work. KMdT reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Adium, Astellas Pharma, AstraZeneca, Bayer, Janssen, Ipsen, Merck Serono, and Pfizer; support for attending meetings and/or travel from Adium, Bayer, Janssen, and Merck Serono; and participation on a data safety monitoring board or advisory board for Adium, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, and Merck Serono outside the submitted work. CN and YL are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. CHP is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; owns stock in Merck & Co., Inc., Rahway, NJ, USA; and has a design patent planned, issued, or pending as an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. JMP reports consulting or advisory role for Astellas Pharma, AstraZeneca/MedImmune, BeiGene, Bristol Myers Squibb, Clovis Oncology, IDEAYA Biosciences, Immunocore, Janssen Oncology, MSD, Pfizer, Roche/Genentech, and VCN Biosciences; research funding from AstraZeneca/MedImmune, BeiGene, Bristol Myers Squibb, Immunocore, Incyte, Janssen Oncology, MSD, Mirati Therapeutics, and Pfizer/EMD Serono; and travel, accommodations, expenses from AstraZeneca Spain, Bristol Myers Squibb, Janssen Oncology, Pfizer, and Roche outside the submitted work. MR, WL, and MK declared no conflicts of interest.

DATA SHARING

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (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: https://externaldatasharing-msd.com/) 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 the 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.

REFERENCES

1. Fizazi K, Gillessen S. Updated treatment recommendations for prostate cancer from the ESMO Clinical Practice Guideline considering treatment intensification and use of novel systemic agents. *Ann Oncol*. 2023;34(6):557-563.
2. Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(9):1119-1134.
3. Schaeffer EM, Srinivas S, Adra N, et al. NCCN Guidelines® Insights: Prostate Cancer, Version 1.2023. *J Natl Compr Canc Netw*. 2022;20(12):1288-1298.
4. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338-351.
5. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2019;381(1):13-24.
6. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. *Lancet*. 2022;399(10336):1695-1707.
7. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med*. 2022;386(12):1132-1142.
8. Graff JN, Antonarakis ES, Hoimes CJ, et al. Pembrolizumab (pembro) plus enzalutamide (enza) for enza-resistant metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE-199 cohorts 4-5. *J Clin Oncol*. 2020;38(suppl 6):15.
9. Yu EY, Berry WR, Gurney H, et al. Pembrolizumab and enzalutamide in patients with abiraterone acetate-pretreated metastatic castration-resistant prostate cancer: cohort C of the phase 1b/2 KEYNOTE-365 study. *Eur Urol Oncol*. 2024;7(3):509-518.
10. Ross AE, Hurley PJ, Tran PT, et al. A pilot trial of pembrolizumab plus prostatic cryotherapy for men with newly diagnosed oligometastatic hormone-sensitive prostate cancer. *Prostate Cancer Prostatic Dis*. 2020;23(1):184-193.
11. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol*. 2019;37(32):2974-2986.
12. Gratzke C, Kwiatkowski M, De Giorgi U, et al. KEYNOTE-991: pembrolizumab plus enzalutamide and androgen deprivation for metastatic hormone-sensitive prostate cancer. *Future Oncol*. 2023;18(37):4079-4087.

13. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.
14. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap*. 1994;23(2):129-138.
15. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570-579.
16. Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology*. 1997;50(6):920-928.
17. US National Library of Medicine. *An Investigational Immunotherapy Study of Nivolumab in Combination with Rucaparib, Docetaxel, or Enzalutamide in Metastatic Castration-resistant Prostate cancer (CheckMate 9KD)*. Bethesda, MD: US National Library of Medicine. Available at https://clinicaltrials.gov/study/NCT03338790?tab=results. Accessed February 23, 2025.
18. Powles T, Yuen KC, Gillessen S, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. *Nat Med*. 2022;28(1):144-153.
19. Graff JN, Burotto M, Fong PC, et al. 1771MO Pembrolizumab (pembro) plus enzalutamide (enza) for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): randomized double-blind phase III KEYNOTE-641 study. *Ann Oncol*. 2023;34:S957.
20. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823-1833.
21. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378(19):1789-1801.
22. *XTANDI® (enzalutamide) capsules, for oral use. XTANDI® (enzalutamide) tablets, for oral use. 10/2020*. Northbrook, IL: Astellas Pharma US, Inc.; 2020.
23. Graff JN, Hoimes CJ, Gerritsen WR, et al. Pembrolizumab plus enzalutamide for metastatic castration-resistant prostate cancer progressing on enzalutamide: cohorts 4 and 5 of the phase 2 KEYNOTE-199 study. *Prostate Cancer Prostatic Dis*. 2025;28(2):411-418.
24. Antonarakis ES, Park SH, Goh JC, et al. 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. *J Clin Oncol*. 2023;41(22):3839-3850.
25. Petrylak DP, Ratta R, Matsubara N, et al. Pembrolizumab plus docetaxel versus docetaxel for previously treated metastatic castration-resistant prostate cancer: the randomized, double-blind, phase III KEYNOTE-921 trial. *J Clin Oncol*. 2025;43(14):1638-1649.
26. Linch MD, Leone G, Wong YNS, et al. Nivolumab and ipilimumab for metastatic prostate cancer with an immunogenic signature: the NEPTUNES multi-centre two-cohort, biomarker-selected phase 2 trial. *J Clin Oncol*. 2024;42(suppl 16):5013.
27. van Wilpe S, Kloots ISH, Slootbeek PHJ, et al. Ipilimumab with nivolumab in molecularly selected patients with castration-resistant prostate cancer: primary analysis of the phase II INSPIRE trial. *Ann Oncol*. 2024;35(12):1126-1137.
28. Sharma P, Krainer M, Saad F, et al. Nivolumab plus ipilimumab for the treatment of post-chemotherapy metastatic castration-resistant prostate cancer (mCRPC): additional results from the randomized phase 2 CheckMate 650 trial. *J Clin Oncol*. 2023;41(suppl 6):22.
29. Sharma P, Pachynski RK, Narayan V, et al. Nivolumab plus ipilimumab for metastatic castration-resistant prostate cancer: preliminary analysis of patients in the CheckMate 650 trial. *Cancer Cell*. 2020;38(4):489-499.e483.
30. Rebuzzi SE, Rescigno P, Catalano F, et al. Immune checkpoint inhibitors in advanced prostate cancer: current data and future perspectives. *Cancers (Basel)*. 2022;14(5):1245.
31. Conteduca V, Brighi N, Schepisi G, et al. Immunogenomic profiles associated with response to life-prolonging agents in prostate cancer. *Br J Cancer*. 2023;129(7):1050-1060.
32. De Bono JS, Joshua AM, Shore ND, et al. KEYNOTE-365 cohort I: phase 1b/2 study of pembrolizumab combined with platinum-containing chemotherapy and chemotherapy alone for treatment-emergent neuroendocrine prostate carcinoma (t-NE). *J Clin Oncol*. 2022;40(suppl 6):TPS218.