Pembrolizumab Plus Docetaxel Versus Docetaxel for Previously Treated Metastatic Castration-Resistant Prostate Cancer: The Randomized, Double-Blind, Phase III KEYNOTE-921 Trial

Daniel P. Petrylak, MD[1]; Raffaele Ratta, MD[2]; Nobuaki Matsubara, MD[3]; Ernesto Korbenfeld, MD[4]; Rustem Gafanov, MD, PhD[5]; Loic Mourey, MD[6]; Tilman Todenhöfer, MD, FEBU[7]; Howard Gurney, MBBS[8]; Gero Kramer, MD[9]; Andries M. Bergman, MD, PhD[10]; Pawel Zalewski, MD[11]; Maria De Santis, MD[9,12]; Andrew J. Armstrong, MD, ScM, FACP[13]; Winald Gerritsen, MD, PhD[14]; Russell Pachynski, MD[15]; Seok Soo Byun, MD[16]; Margitta Retz, MD, PhD[17]; Eric Levesque, MD, PhD[18]; Ray McDermott, MD, PhD[19]; Sergio Bracarda, MD[20]; Ray Manneh, MD[21]; Meital Levartovsky, MD[22]; Xin Tong Li, PhD[23]; Charles Schloss, MD[23]; Christian H. Poehlein, MD[23]; and Karim Fizazi, MD, PhD[24]

DOI https://doi.org/10.1200/JCO-24-01283

ABSTRACT

PURPOSE The standard of care for metastatic castration-resistant prostate cancer (mCRPC) after second-generation androgen receptor pathway inhibitor (ARPI) therapy is still docetaxel. The randomized, double-blind, phase III KEYNOTE-921 trial (Clinicaltrials.gov identifier: NCT03834506) evaluated the efficacy and safety of pembrolizumab or placebo plus docetaxel for previously treated mCRPC.

METHODS Adults with mCRPC who progressed after androgen-deprivation therapy and one ARPI were randomly assigned 1:1 to pembrolizumab or placebo plus docetaxel with concomitant prednisone. Dual primary end points were radiographic progression-free survival (rPFS) by blinded independent central review per Prostate Cancer Working Group 3–modified RECIST 1.1 and overall survival (OS). Safety was a secondary end point.

RESULTS Between May 30, 2019, and June 17, 2021, 515 participants were randomly assigned to pembrolizumab plus docetaxel and 515 to placebo plus docetaxel. Median time from random assignment to data cutoff date (June 20, 2022) at final analysis (FA) was 22.7 months (range, 12.1-36.7). At first interim analysis (data cutoff date: September 27, 2021), median rPFS was 8.6 months (95% CI, 8.3 to 10.2) with pembrolizumab plus docetaxel versus 8.3 months (95% CI, 8.2 to 8.5) with placebo plus docetaxel (hazard ratio [HR], 0.85 [95% CI, 0.71 to 1.01]; $P = .03$). At FA, median OS was 19.6 months (95% CI, 18.2 to 20.9) versus 19.0 months (95% CI, 17.9 to 20.9), respectively (HR, 0.92 [95% CI, 0.78 to 1.09]; $P = .17$). Grade ≥3 treatment-related adverse events occurred in 43.2% of participants who received pembrolizumab plus docetaxel and 36.6% of participants who received placebo plus docetaxel. Two and seven participants, respectively, died due to a treatment-related adverse event. Pneumonitis was the most common immune-mediated adverse event (7.0% *v* 3.1%).

CONCLUSION The addition of pembrolizumab to docetaxel did not significantly improve efficacy outcomes for participants with previously treated mCRPC. The current standard of care remains unchanged.

ACCOMPANYING CONTENT

Editorial, p. 1617
Appendix
Data Supplement
Protocol

Accepted January 7, 2025
Published March 5, 2025

J Clin Oncol 43:1638-1649

View Online Article

INTRODUCTION

Taxane chemotherapy is a key treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC) following disease progression after a second-generation androgen receptor pathway inhibitor (ARPI).[1,2] The pivotal, randomized, phase III TAX 327 study and the prospective, randomized, phase III Southwest Oncology Group 99-16 study were both conducted before the advent of ARPI therapy, establishing docetaxel as a new standard of care for patients with mCRPC on the basis of overall survival (OS) benefits versus mitoxantrone plus prednisone.[3,4]

CONTEXT

Key Objective

Does the addition of pembrolizumab to docetaxel improve efficacy outcomes for patients with previously treated metastatic castration-resistant prostate cancer without a major increase in toxicity?

Knowledge Generated

Pembrolizumab plus docetaxel did not significantly improve radiographic progression-free survival or overall survival versus placebo plus docetaxel in the randomized, double-blind, phase III KEYNOTE-921 study. The addition of pembrolizumab to docetaxel did not result in a notable increase in adverse events, with the exception of pneumonitis.

Relevance *(A. Necchi)*

Taxane chemotherapy is unable to sensitize prostate cancer to immune checkpoint inhibitors, resulting in another negative trial with immunotherapy in prostate cancer. Further trials with immune checkpoint inhibitors in unselected patients should be discouraged.*

*Relevance section written by *JCO* Associate Editor Andrea Necchi, MD.

Currently, docetaxel is recommended as an upfront or post-ARPI regimen, and cabazitaxel is recommended in men who have already received docetaxel.[1-3,5,6] Combinations of docetaxel and targeted agents or other therapies have failed to show consistent evidence of superior survival over docetaxel alone in phase III trials for mCRPC.[7-13] Given the relatively short progression-free survival (PFS) times across available systemic therapies for mCRPC, including taxanes, an urgent clinical need remains for more efficacious therapeutic options for this patient population.

Immune checkpoint inhibitors have shown nominal antitumor activity in advanced prostate cancer, although no checkpoint inhibitor–based combination has yet been identified as superior to the standard of care in a randomized trial setting for mCRPC. In a phase Ia dose-escalation and dose-expansion study, atezolizumab monotherapy in 35 participants with heavily pretreated mCRPC resulted in a prostate-specific antigen (PSA) response rate of 8.6%.[14] In a cohort of the phase II CheckMate 9KD study that included 54 participants with chemotherapy-naïve mCRPC and one or two previous ARPI regimens, nivolumab plus docetaxel showed antitumor activity (objective response rate [ORR] among 31 evaluable participants, 38.7% [95% CI, 21.8 to 57.8]), radiographic PFS (rPFS; median, 8.5 months), and OS (median, 16.2 months).[15] Pembrolizumab, an anti–PD-1 antibody, demonstrated durable antitumor activity and an acceptable safety profile as monotherapy for participants with mCRPC previously treated with docetaxel and abiraterone and/or enzalutamide in Cohorts 1-3 of the KEYNOTE-199 study.[16]

Immune checkpoint inhibitors, including pembrolizumab, have been successfully combined with chemotherapy to prolong OS and PFS in other tumor types. Although monotherapy had limited activity in prostate cancer, we hypothesized that adding pembrolizumab to the established therapy docetaxel may have a role in mCRPC treatment. In Cohort B of the phase Ib/II KEYNOTE-365 study, pembrolizumab plus docetaxel in participants with mCRPC previously treated with abiraterone or enzalutamide showed an ORR and PSA response that warranted further investigation in a randomized setting. The safety profile of this combination was consistent with the known profiles of each individual agent.[17] Therefore, the KEYNOTE-921 study (ClinicalTrials.gov identifier: NCT03834506) was designed to evaluate pembrolizumab or placebo plus docetaxel as a treatment for mCRPC after previous ARPI therapy.

METHODS

Study Design

KEYNOTE-921 is a randomized, double-blind, multicenter, placebo-controlled, phase III study conducted at 224 medical centers globally. Eligible participants were randomly allocated (1:1) using a central interactive voice-response system to pembrolizumab plus docetaxel or placebo plus docetaxel. Randomization was stratified by previous ARPI therapy (abiraterone yes *v* no) and sites of metastasis (bone only *v* liver *v* other). Participants and investigators were blinded to study treatment assignment.

Participant Population

Eligible participants had histologically or cytologically confirmed adenocarcinoma of the prostate that progressed during androgen-deprivation therapy or after bilateral orchiectomy ≤6 months before screening as determined by investigator in soft tissue per RECIST version 1.1 (RECIST 1.1), in bone per Prostate Cancer Working Group 3 (PCWG3), or by PSA levels. Participants were male, age 18 years and older, and had current evidence of metastatic disease either on bone scans or in soft tissues by computed tomography or

magnetic resonance imaging, adequate organ function, an Eastern Cooperative Oncology Group performance status of 0 or 1, and ongoing androgen deprivation with serum testosterone <0.50 ng/mL (<2.0 nM). Participants had either disease progression after or intolerance to one previous ARPI (abiraterone, enzalutamide, apalutamide, or darolutamide) in the metastatic hormone-sensitive or castration-resistant setting. Key exclusion criteria included previous radium or radiopharmaceuticals. Previous docetaxel for metastatic disease was only permitted if administered in the hormone-sensitive setting for ≥six cycles with no disease progression ≤1 year after the last dose.

Treatment

Participants received docetaxel 75 mg/m² intravenously once every 3 weeks for ≤10 cycles, prednisone 5 mg orally twice daily concomitantly with docetaxel, and either pembrolizumab 200 mg or matched placebo intravenously once every 3 weeks for ≤35 cycles (approximately 2 years). A minimum of six cycles of docetaxel was recommended unless specific discontinuation criteria were met. Pembrolizumab interruption or discontinuation, but not dose reduction, was permitted. Docetaxel administration could be interrupted, resumed at full dose or at a reduced dose of 60 mg/m², or discontinued per protocol specifications. Dexamethasone (or equivalent corticosteroid) premedication 12, 3, and 1 hour before docetaxel administration was recommended; local standard-of-care premedication was permitted. Prednisone was discontinued after cessation of docetaxel. Participants who attained a confirmed complete response and received ≥eight cycles of study treatment (including two cycles beyond initial documentation of a complete response) could discontinue study treatment. Participants could also discontinue study treatment upon request, because of confirmed radiographic disease progression, or unacceptable toxicity. Participants who discontinued pembrolizumab, placebo, or docetaxel because of treatment-related adverse events could continue to receive the other study drug in consultation with the study sponsor. Participants who stopped study treatment continued to be followed up as part of the study unless they withdrew consent.

End Points

The dual primary end points were rPFS by blinded independent central review per PCWG3-modified RECIST 1.1 and OS. A key secondary end point was time to initiation of the first subsequent anticancer therapy (TFST). Secondary end points included safety, the proportion of participants with PSA response, ORR, time to PSA progression, and duration of response (DOR). Definitions of all end points and detailed assessments and procedures are available in the Data Supplement (online only).

Study Oversight

All participants provided written informed consent. The appropriate local or national ethics body for each participating center approved the study protocol and all amendments. The study was conducted in accordance with Good Clinical Practice guidelines. An external data monitoring committee oversaw the study, assessed safety at regular interim analyses, and assessed efficacy at prespecified interim analyses. The study sponsor, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc (Rahway, NJ), participated in the study design, data collection, data analysis, data interpretation, the writing of this report, and maintenance of the study database.

Statistical Analysis

Event rates over time were estimated by the nonparametric Kaplan-Meier method for rPFS, OS, TFST, time to PSA progression, and DOR. Hazard ratios (HRs) and 95% CI were estimated with a stratified Cox regression model with Efron's method of tie handling and with treatment group as the single covariate. Between-treatment differences were evaluated using a stratified log-rank test. The planned study sample size was approximately 1,000 participants (500 in each treatment group). Formal hypothesis testing of rPFS was conducted at the first prespecified interim analysis (IA1; data cutoff date of September 27, 2021) and formal hypothesis testing of OS was conducted at the final analysis (FA; data cutoff date of June 20, 2022). The study had at least 90% power to detect superior rPFS with pembrolizumab plus docetaxel versus placebo plus docetaxel after at least 468 events at an initial overall $\alpha = .005$ (one-sided) if the underlying constant HR between treatment groups was 0.70, and approximately 90% power to detect superior OS after at least 549 events at an initial overall $\alpha = .02$ (one-sided) if the underlying constant HR between treatment groups was 0.75. The overall type I error rate was strongly controlled at 2.5% (one-sided) using the graphical method of Maurer and Bretz, with 0.5% allocated to test rPFS and 2.0% allocated to test OS. The *P* value boundary for significance was .005 (one-sided) for rPFS at IA1 and .0174 (one-sided) for OS at FA. We used SAS version 9.4 for all statistical analyses.

Efficacy end points were assessed in the intention-to-treat population, defined as all randomly assigned participants. Objective response was assessed in all participants in the intention-to-treat population who had measurable disease at baseline per PCWG3-modified RECIST 1.1. Safety was assessed in the as-treated population, defined as all randomly assigned participants who received ≥one dose of study treatment.

RESULTS

A total of 1,362 participants were screened for the study, of whom 332 did not meet study eligibility criteria. Between May 30, 2019, and June 17, 2021, 1,030 participants (intention-to-treat population) were randomly allocated to receive pembrolizumab plus docetaxel (n = 515) or placebo plus docetaxel (n = 515; Fig 1). Participant demographics and baseline characteristics were generally balanced between groups (Table 1). The median age in each group was 71 years

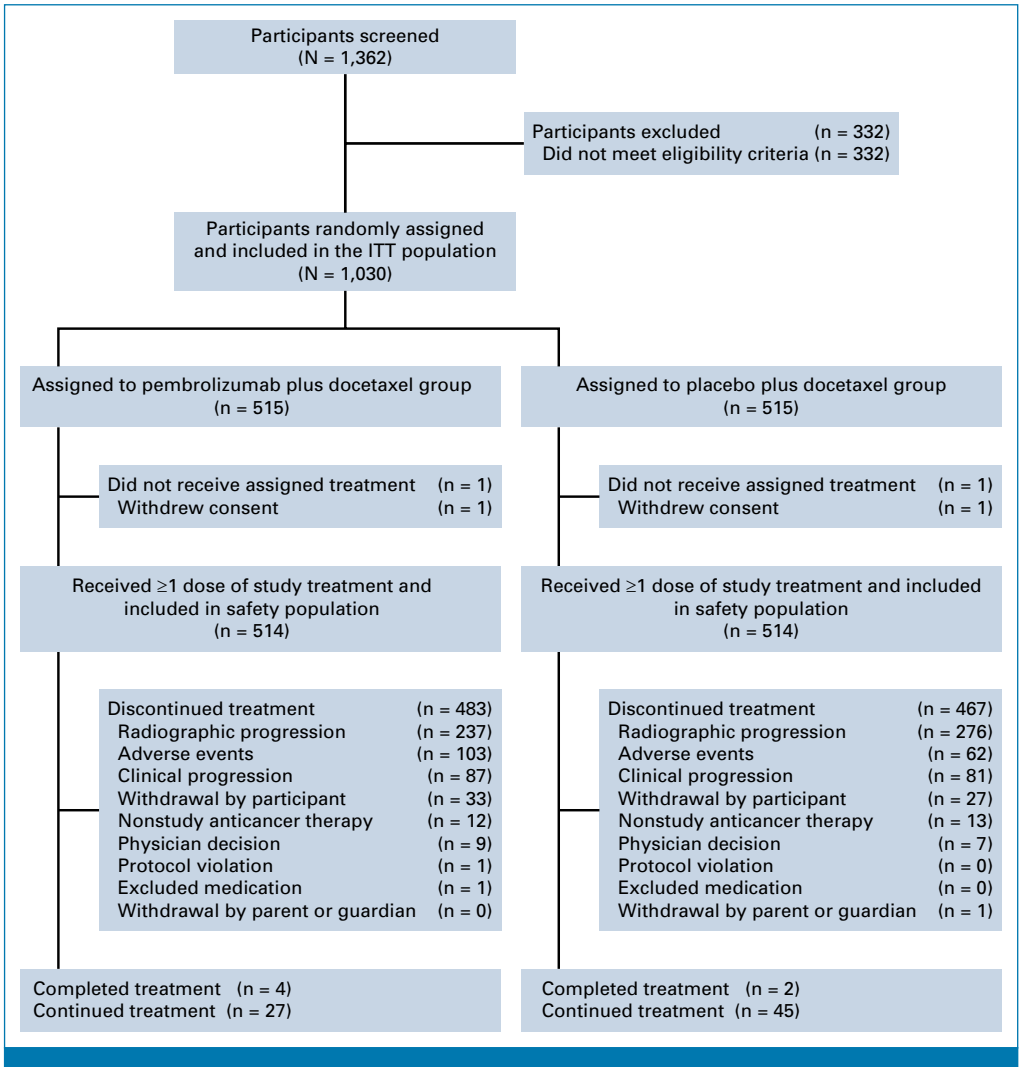

FIG 1. CONSORT diagram. ITT, intention-to-treat.

(range, 43-89 for the pembrolizumab plus docetaxel group; range, 47-92 for the placebo plus docetaxel group). Approximately half of the participants in the pembrolizumab plus docetaxel (54.0%) and placebo plus docetaxel (53.8%) groups had received previous abiraterone, including one and two participants who received both previous abiraterone and enzalutamide. PD-L1–positive disease was identified by immunohistochemistry in 24.5% and 19.8% participants in each group, respectively. Finally, 39.4% participants in the pembrolizumab plus docetaxel group and 42.9% participants in the placebo plus docetaxel group had measurable disease per PCWG-modified RECIST 1.1 at baseline. At IA1, the median follow-up (defined as the time from random assignment until the data cutoff date of September 27, 2021) was 14.0 months (range, 3.4-28.0). Median follow-up at FA (data cutoff date of June 20, 2022) was 22.7 months (range, 12.1-36.7). The median number of pembrolizumab or placebo cycles was 12 (range, 1-35) in the respective groups; both treatment groups received a median number of nine cycles of docetaxel (range, 1-12 in the pembrolizumab plus docetaxel group and 1-10 in the placebo plus docetaxel group; Data Supplement, Table S1). At FA, 94.0% of participants in the pembrolizumab plus docetaxel group and 90.9% in the placebo plus docetaxel group had discontinued study treatment, 0.8% and 0.4% of participants had completed study treatment, and 64.3% and 63.1% of participants had received subsequent anticancer therapy, respectively. Cabazitaxel was the most common subsequent therapy (40.0% and 38.6% of participants, respectively; Data Supplement, Table S2).

At IA1, 240 (46.6%) participants in the pembrolizumab plus docetaxel group and 269 (52.2%) participants in the placebo plus docetaxel group had rPFS events. Median rPFS was 8.6 months (95% CI, 8.3 to 10.2) versus 8.3 months (95% CI, 8.2 to 8.5), respectively (HR, 0.85 [95% CI, 0.71 to 1.01]; $P = .03$; Fig 2A). No further formal statistical testing was performed for this primary end point per the statistical analysis plan. No notable differences in rPFS across most prespecified subgroups were observed, although the sample size in some subgroups, such as participants with liver metastasis, was small (Fig 2B). At IA1, among participants

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

Characteristic	Pembrolizumab Plus Docetaxel (n = 515)	Placebo Plus Docetaxel (n = 515)
Age, years, median (range)	71 (43-89)	71 (47-92)
≥65, No. (%)	395 (76.7)	410 (79.6)
Male sex, No. (%)	515 (100.0)	515 (100.0)
Race, No. (%)		
American Indian or Alaska Native	6 (1.2)	8 (1.6)
Asian	78 (15.1)	76 (14.8)
Black or African American	13 (2.5)	13 (2.5)
Multiple	15 (2.9)	18 (3.5)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0
White	401 (77.9)	399 (77.5)
Missing	1 (0.2)	1 (0.2)
ECOG performance status score, No. (%)		
0	298 (57.9)	286 (55.5)
1	212 (41.2)	227 (44.1)
4[a]	1 (0.2)	0
Missing	4 (0.8)	2 (0.4)
Geographic region, No. (%)		
North America	67 (13.0)	77 (15.0)
Western Europe	235 (45.6)	222 (43.1)
Rest of the world	213 (41.4)	216 (41.9)
Previous ARPI, No. (%)		
Any abiraterone	278 (54.0)	277 (53.8)
Abiraterone only	277 (53.8)	275 (53.4)
Abiraterone and enzalutamide	1 (0.2)	2 (0.4)
Enzalutamide only	231 (44.9)	229 (44.5)
None	6 (1.2)	7 (1.4)
Previous docetaxel,[b] No. (%)		
Yes	69 (13.4)	59 (11.5)
No	446 (86.6)	456 (88.5)
Type of metastasis at baseline, No. (%)		
Bone only	268 (52.0)	239 (46.4)
Liver	34 (6.6)	33 (6.4)
Other	213 (41.4)	243 (47.2)
PSA value, ng/mL, median (range)	30.4 (0.1-3,586.0)	28.7 (0.1-5,000.0)
Gleason sum, No. (%)		
≤7	183 (35.5)	151 (29.3)
≥8	319 (61.9)	353 (68.5)
Unknown	13 (2.5)	11 (2.1)
PD-L1 status, No. (%)		
Positive	126 (24.5)	102 (19.8)
Negative	346 (67.2)	372 (72.2)
Not evaluable or unknown	43 (8.3)	41 (8.0)
Disease measurable by RECIST v1.1, No. (%)	203 (39.4)	221 (42.9)

Abbreviations: ARPI, second-generation androgen receptor pathway inhibitor; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

[a]Protocol violation.

[b]Previous docetaxel for metastatic disease was only permitted if administered in the hormone-sensitive setting for ≥six cycles with no disease progression ≤1 year after the last dose.

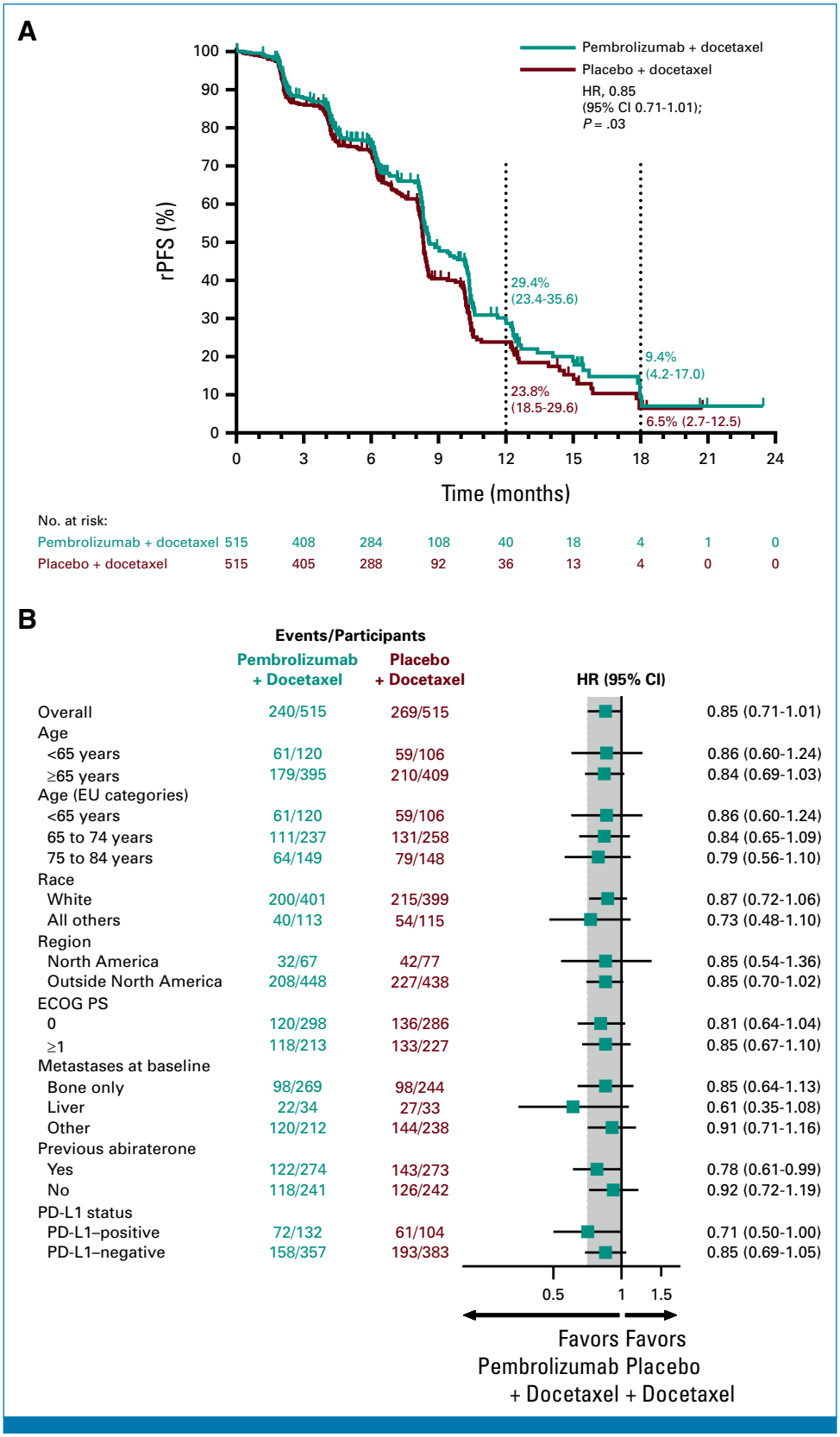

FIG 2. rPFS (dual primary end point) in the intention-to-treat population and key subgroups. (A) Kaplan-Meier estimates of rPFS in the intention-to-treat population and (B) key subgroups at IA1 per PCWG-modified RECIST 1.1 by masked independent central review. ECOG, Eastern Cooperative Oncology Group; EU, European Union; HR, hazard ratio; IA1, first prespecified interim analysis; PCWG, Prostate Cancer Working Group; PS, performance status; rPFS, radiographic progression-free survival.

with PD-L1–positive disease, median rPFS was 8.3 months (95% CI, 8.1 to 9.9) with pembrolizumab plus docetaxel versus 7.4 months (95% CI, 6.2 to 8.3) with placebo plus docetaxel (HR, 0.71 [95% CI, 0.50 to 1.00]; Data Supplement, Fig S1A). Among participants with PD-L1–negative disease, median rPFS was 9.0 months (95% CI, 8.4 to 10.3) versus 8.3 months (95% CI, 8.3 to 8.5; HR, 0.85 [95% CI, 0.69 to 1.05]; Data Supplement, Fig S1B). Among participants with nonevaluable or unknown PD-L1 status, median rPFS was 7.2 months (95% CI, 6.2 to 10.3) versus 8.5 months (95% CI, 6.1 to 10.5) in this population (HR, 1.05 [95% CI, 0.46 to 2.42]; Data Supplement, Fig S1C).

At FA, 275 (53.4%) participants in the pembrolizumab plus docetaxel group and 288 (55.9%) in the placebo plus docetaxel group had died; median OS was 19.6 months (95% CI, 18.2 to 20.9) versus 19.0 months, respectively (95% CI, 17.9 to 20.9; HR, 0.92 [95% CI, 0.78 to 1.09]; $P = .17$; Fig 3A). OS results were generally consistent across prespecified subgroups by participant demographic and baseline disease characteristics (Fig 3B). As PD-L1 CPS could be updated in the database up until the final data cutoff date, the total number of participants classified as having PD-L1–positive disease was slightly different at IA1 and FA. Among participants with PD-L1–positive mCRPC, median OS was 19.8 months (95% CI, 16.2 to 22.0) in the pembrolizumab plus docetaxel group versus 14.9 months (95% CI, 12.4 to 18.2) in the placebo plus docetaxel group (HR, 0.71 [95% CI, 0.51 to 0.98]; Data Supplement, Fig S2A). Among participants with PD-L1–negative disease, median OS was 19.6 months (95% CI, 18.0 to 21.2) versus 20.8 months (95% CI, 18.7 to 23.8), respectively (HR, 0.99 [95% CI, 0.81 to 1.21]; Data Supplement, Fig S2B). Among participants with nonevaluable or unknown PD-L1 status, median OS in this population was 19.4 months (95% CI, 15.8 to not reached) versus 18.7 months, respectively (95% CI, 13.9 to 24.1; HR, 0.72 [95% CI, 0.38 to 1.34]; Data Supplement, Fig S2C).

At IA1, a total of 296 (57.5%) participants in the pembrolizumab plus docetaxel group and 327 (63.5%) in the placebo plus docetaxel group had received subsequent anticancer therapy or died. Median TFST was 10.7 months (95% CI, 10.4 to 11.1) versus 10.4 months, respectively (95% CI, 9.7 to 11.1; HR, 0.86 [95% CI, 0.74 to 1.01]; Data Supplement, Fig S3). At FA, in the intention-to-treat population, 331 (64.3%) events in the pembrolizumab plus docetaxel group and 341 (66.2%) events in the placebo plus docetaxel group had a PSA progression event. Median time to PSA progression was 6.9 months (95% CI, 6.2 to 7.6) versus 7.0 months, respectively (95% CI, 6.3 to 7.6; HR, 0.96 [95% CI, 0.82 to 1.12]; Data Supplement, Fig S4). A total of 474 (92.0%) in the pembrolizumab plus docetaxel group and 486 (94.4%) in the placebo plus docetaxel group had a baseline PSA measurement. Confirmed PSA response was observed in 211/474 (44.5%; 95% CI, 40.0 to 49.1) participants with pembrolizumab plus docetaxel and in 222/486 (45.7%; 95% CI, 41.2 to 50.2) with placebo plus docetaxel.

Among participants in the intention-to-treat population who had measurable disease at baseline, four (2.0%) had a complete response and 64 (31.5%) had a partial response with pembrolizumab plus docetaxel, and four (1.8%) had a complete response and 74 (33.5%) had a partial response with placebo plus docetaxel (Table 2). The ORR was 33.5% (95% CI, 27.0 to 40.4) and 35.3% (95% CI, 29.0 to 42.0), respectively. Median DOR was 6.3 months (range, 3.4+ to 21.2) and 6.2 months (range, 2.0+ to 13.1), respectively.

A total of 514 participants in each treatment group received ≥one dose of study treatment and were included in the as-treated population. Median treatment duration was 7.8 months (range, 0.0-26.8) with pembrolizumab plus docetaxel and 8.1 months (range, 0.0-24.2) with placebo plus docetaxel (Data Supplement, Table S1). Adverse events of any cause resulting in treatment discontinuation are provided in the Data Supplement (Table S3), most commonly pneumonitis (2.9% *v* 0.8%), peripheral sensory neuropathy (2.5% *v* 3.3%), diarrhea (1.8% *v* 1.2%), and fatigue (1.0% *v* 1.8%). Adverse events of any cause leading to death occurred in 28 (5.4%) participants in each treatment group, most commonly pneumonia (n = 3) in the pembrolizumab plus docetaxel group and COVID-19 pneumonia (n = 5) in the placebo plus docetaxel group (Data Supplement, Table S4).

A total of 486 (94.6%) participants who received pembrolizumab plus docetaxel and 488 (94.9%) who received placebo plus docetaxel had treatment-related adverse events (grade ≥3, 43.2% and 36.6%, respectively). The most common events of any grade were alopecia (34.6% *v* 36.6%), diarrhea (34.6% *v* 30.7%), and fatigue (30.9% *v* 30.9%; Table 3). Two treatment-related deaths occurred in the pembrolizumab plus docetaxel group (one each because of pneumonitis and interstitial lung disease) and seven in the placebo plus docetaxel group (one each because of clostridial sepsis, febrile neutropenia, influenzal pneumonia, neck abscess, pneumonia, respiratory failure, and urosepsis). Serious treatment-related adverse events occurred in 20.2% and 15.2% of participants, respectively, most commonly (≥2% of participants in any group) febrile neutropenia (5.3% *v* 4.1%) in both groups, pneumonitis in the pembrolizumab plus docetaxel group (2.9% *v* 1.0%), and pneumonia in the placebo plus docetaxel group (1.4% *v* 1.9%; Data Supplement, Table S5).

Immune-mediated adverse events (on the basis of a list of preferred terms intended to capture known risks of pembrolizumab and considered regardless of attribution to study treatment by the investigator) and infusion reactions occurred in 19.1% of participants who received pembrolizumab plus docetaxel and 10.5% participants who received placebo plus docetaxel, most commonly pneumonitis (7.0% *v* 3.1%) and hypothyroidism (6.4% *v* 3.3%; Data Supplement, Table S6). Grade ≥3 immune-mediated adverse events occurred in 6.0% and 1.2% of participants, respectively, most commonly pneumonitis (3.3%) and severe skin reactions (1.2%) with

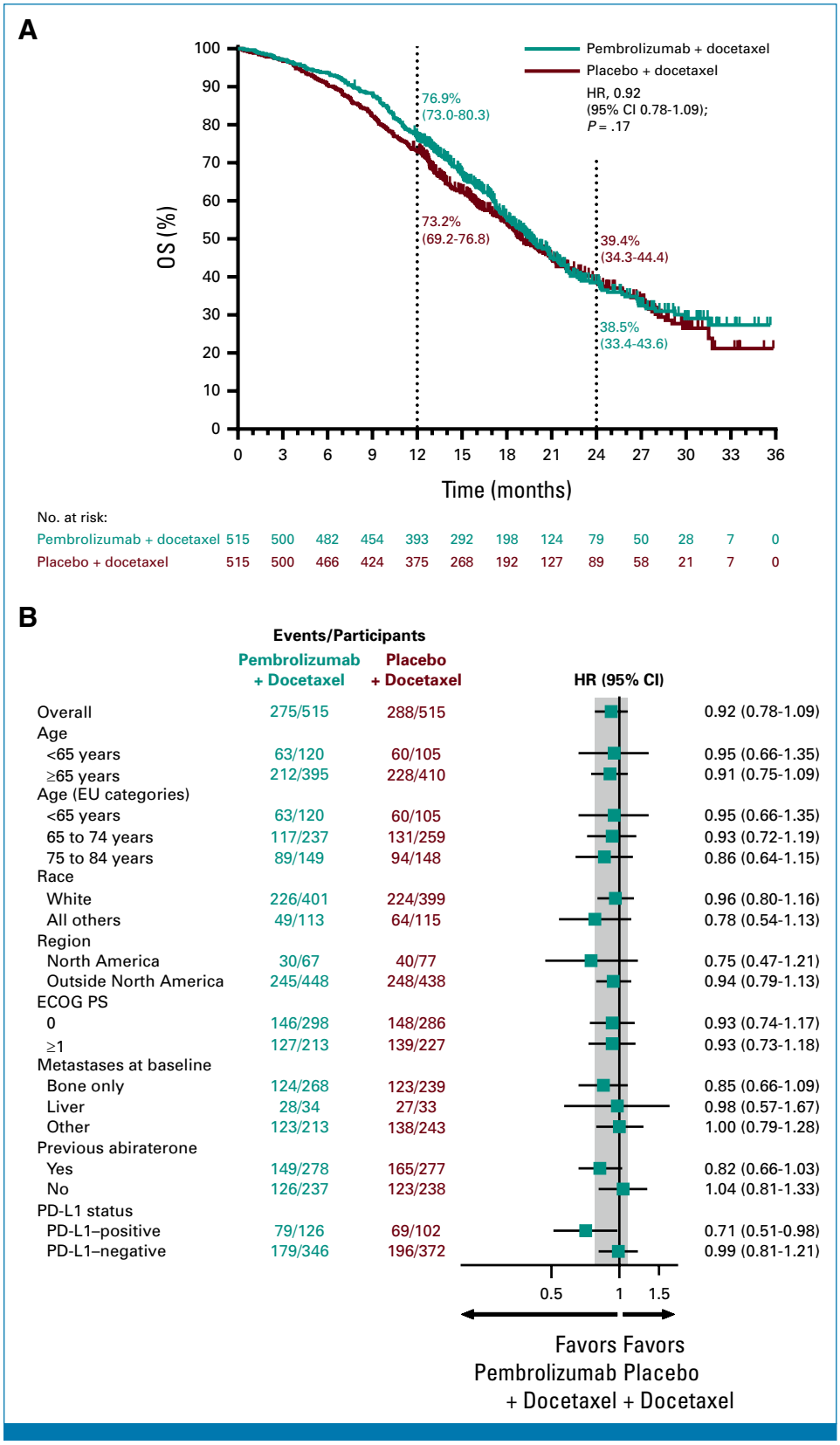

FIG 3. OS (dual primary end point) in the intention-to-treat population and key subgroups. (A) Kaplan-Meier estimates of OS in the intention-to-treat population and (B) key subgroups at FA. ECOG, Eastern Cooperative Oncology Group; EU, European Union; FA, final analysis; HR, hazard ratio; OS, overall survival; PS, performance status.

TABLE 2. Best Overall Response in the Intention-to-Treat Population With Measurable Disease at Baseline

Parameter	Pembrolizumab Plus Docetaxel (n = 203)	Placebo Plus Docetaxel (n = 221)
ORR, No. (%; 95% CI)	68 (33.5; 27.0 to 40.4)	78 (35.3; 29.0 to 42.0)
Best overall response, No. (%)		
Complete response	4 (2.0)	4 (1.8)
Partial response	64 (31.5)	74 (33.5)
Stable disease	102 (50.2)	99 (44.8)
Progressive disease	27 (13.3)	33 (14.9)
Nonevaluable[a]	1 (0.5)	2 (0.9)
No assessment[b]	5 (2.5)	9 (4.1)
Proportion of participants with a complete or partial response or stable disease for ≥6 months, No. (%; 95% CI)	117 (57.6; 50.5 to 64.5)	133 (60.2; 53.4 to 66.7)
DOR, months, median (range)	6.3 (3.4+ to 21.2)	6.2 (2.0+ to 13.1)

NOTE. Response was assessed according to PCWG-modified RECIST version 1.1 by means of blinded independent central review of radiologic imaging. Percentages may not total 100 because of rounding.
Abbreviations: DOR, duration of response; ORR, objective response rate; PCWG, Prostate Cancer Working Group.
[a]Postbaseline assessment(s) available, but not evaluable.
[b]No postbaseline assessment available for response evaluation.

pembrolizumab plus docetaxel and pneumonitis (0.4%) and hypophysitis (0.4%) with placebo plus docetaxel.

DISCUSSION

The phase III KEYNOTE-921 study did not meet the predefined criteria for superiority of pembrolizumab plus docetaxel versus placebo plus docetaxel for the dual primary end points of rPFS and OS in participants with chemotherapy-naïve mCRPC with disease progression after or intolerance to ARPI. Outcomes were consistent between the two treatments across prespecified subgroups, and across secondary efficacy end points. In the pembrolizumab plus docetaxel group, median OS in participants with PD-L1–positive mCRPC was similar to that observed for the entire intention-to-treat population. In the placebo plus docetaxel group, median OS in participants with PD-L1–positive mCRPC appeared shorter than that observed for the entire intention-to-treat population. The addition of pembrolizumab to docetaxel generally did not result in a notable increase in any-cause adverse

TABLE 3. Summary of Treatment-Related Adverse Events in the As-Treated Population at Final Analysis

	Pembrolizumab Plus Docetaxel (n = 514), No. (%)		Placebo Plus Docetaxel (n = 514), No. (%)	
Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event	508 (98.8)	312 (60.7)	505 (98.2)	299 (58.2)
Any treatment-related adverse event	486 (94.6)	222 (43.2)	488 (94.9)	188 (36.6)
Treatment-related adverse events occurring in ≥10% of participants in either treatment group				
Alopecia	178 (34.6)	1 (0.2)	188 (36.6)	3 (0.6)
Diarrhea	178 (34.6)	17 (3.3)	158 (30.7)	10 (1.9)
Fatigue	159 (30.9)	14 (2.7)	159 (30.9)	16 (3.1)
Peripheral sensory neuropathy	127 (24.7)	6 (1.2)	94 (18.3)	6 (1.2)
Asthenia	115 (22.4)	10 (1.9)	102 (19.8)	7 (1.4)
Nausea	107 (20.8)	4 (0.8)	111 (21.6)	0
Anemia	103 (20.0)	14 (2.7)	90 (17.5)	17 (3.3)
Decreased appetite	75 (14.6)	5 (1.0)	67 (13.0)	3 (0.6)
Dysgeusia	68 (13.2)	0	70 (13.6)	0
Peripheral edema	57 (11.1)	0	68 (13.2)	1 (0.2)
Constipation	52 (10.1)	0	34 (6.6)	1 (0.2)

NOTE. Adverse events are presented according to the Medical Dictionary for Regulatory Affairs preferred terminology. As-treated population includes all participants who received ≥one dose of trial treatment.

events, treatment-related adverse events, or treatment-related deaths, with the exception of any-cause and immune-mediated pneumonitis. No new safety signals were observed for this combination.

rPFS and OS with pembrolizumab plus docetaxel in KEYNOTE-921 were consistent with previous observations for this regimen in Cohort B of the phase Ib/II KEYNOTE-365 study (median rPFS, 8.5 months [95% CI, 8.3 to 10]; median OS, 20.2 months [95% CI, 17 to 24]).[17] A slightly higher proportion of participants with measurable disease at baseline had a response with pembrolizumab plus docetaxel in KEYNOTE-921 compared with KEYNOTE-365 (12/52 participants; 23% [95% CI, 13 to 37]).[17] The adverse event profile of pembrolizumab plus docetaxel was also generally consistent with observations in KEYNOTE-365, except for slightly lower overall incidences of common adverse events such as any-grade diarrhea, alopecia, and fatigue in KEYNOTE-921.

Although no direct comparisons can be made between KEYNOTE-921 and the CheckMate 9KD study, results for the pembrolizumab plus docetaxel regimen in KEYNOTE-921 were in line with reported efficacy and safety outcomes for nivolumab plus docetaxel in the subgroup of participants who had received one or two previous ARPI therapies.[15] It is now known that the phase III CheckMate 7DX study of nivolumab plus docetaxel versus placebo plus docetaxel in advanced mCRPC also did not meet its primary end points of rPFS and OS, and was stopped (data not published as of this writing). Taken together, these findings suggest that anti–PD-1 therapy plus docetaxel may not be an effective therapeutic approach for an all-comer population in this disease, likely because of the poor immunogenicity of the prostate tumor microenvironment and high infiltration of immunosuppressive cells.[18,19] Immune checkpoints expressed on regulatory T cells or myeloid-derived suppressor cells may be more promising future targets than the PD-1/PD-L1 signaling axis in prostate cancer.

The survival benefits of docetaxel therapy were initially established in the first-line mCRPC setting in two randomized phase III studies before the introduction of ARPIs.[3,4,7] In the current landscape, docetaxel is commonly used upfront for de novo mCRPC or after ARPI therapy.[1,2] Although limited prospective clinical trial data are available, previous analysis of docetaxel activity in men with mCRPC after abiraterone failure reported a median time to PSA progression of 7.6 months (95% CI, 5.0 to not estimable), in line with the median PSA progression of 7.0 months with placebo plus docetaxel observed in our study.[20] KEYNOTE-921 sets a benchmark for median OS of 19.0 months and for median rPFS of 8.3 months for docetaxel in the post-ARPI setting. These results are numerically higher than reported in limited available real-world observations,[21] and may be informative to the design of future trials. Nearly 40% of participants in KEYNOTE-921 received subsequent cabazitaxel therapy, which may have partially contributed to longer OS compared with past studies. Potentially poor survival outcomes in participants with PD-L1–positive mCRPC who received placebo plus docetaxel were noted compared with participants with PD-L1–negative mCRPC who received placebo plus docetaxel. Evidence in the literature suggests a correlation between increased PD-L1 expression and disease aggressiveness in primary prostate cancer,[22] indicating a less favorable prognosis.

A limitation of this study design was that it was not powered to formally conduct hypothesis testing around biomarker-defined subgroups and no definitive conclusions can be made regarding whether this combination has usefulness for select subgroups of patients with mCRPC. Further study with a larger sample size and longer follow-up may have helped identify a subset of participants who benefitted from pembrolizumab plus docetaxel. Known biomarkers associated with increased pembrolizumab efficacy across tumor types include microsatellite instability-high status and high tumor mutational burden.[23,24] Additional potential biomarkers, such as CDK12 inactivation, DNA polymerase epsilon mutations, and homologous recombination deficiency,[25] require future investigation.

New efficacious therapeutic options for mCRPC remain an unmet need. Real-world data indicate that the median OS of patients with newly diagnosed mCRPC is <30 months in the United States and Europe,[26-28] and the most recent progress has occurred in the hormone-sensitive setting.[29] Next-generation studies should investigate novel agents and combinations for this disease.

AFFILIATIONS

[1]Yale Cancer Center, New Haven, CT
[2]Hopital Foch, Suresnes, France
[3]National Cancer Center Hospital East, Chiba, Japan
[4]Hospital Britanico de Buenos Aires, Buenos Aires, Argentina
[5]Russian Scientific Center of Roentgenoradiology, Moscow, Russia
[6]Institut Claudius Regaud IUCT Oncopole, Toulouse, France
[7]Studienpraxis Urologie, Nürtingen, Germany
[8]Macquarie University, Sydney, Australia
[9]Department of Urology, Medical University of Vienna, Vienna, Austria
[10]Netherlands Cancer Institute, Amsterdam, the Netherlands
[11]Lakeridge Health, Oshawa, ON, Canada
[12]Department of Urology, Charite Universitaetsmedizin Berlin, Berlin, Germany
[13]Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC
[14]Radboud University Medical Center, Nijmegen, the Netherlands
[15]Washington University School of Medicine, St Louis, MO
[16]Seoul National University Bundang Hospital, Seongnam, South Korea
[17]Rechts der Isar Medical Center, Technical University Munich, Munich, Germany
[18]CHU de Québec-Université Laval-Hôtel-Dieu de Québec, Québec City, QC, Canada
[19]St Vincent's University Hospital, Cancer Trials Ireland, Dublin, Ireland
[20]Azienda Ospedaliera Santa Maria Terni, Terni, Italy

[21]Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia
[22]Chaim Sheba Medical Center, Ramat Gan, Israel
[23]Merck & Co, Inc, Rahway, NJ
[24]Institut Gustave Roussy, University of Paris Saclay, Villejuif, France

CORRESPONDING AUTHOR

Daniel P. Petrylak, MD; e-mail: daniel.petrylak@yale.edu.

SUPPORT

Supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ.

CLINICAL TRIAL INFORMATION

NCT03834506 (KEYNOTE-921)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-01283.

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: 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.

AUTHOR CONTRIBUTIONS

Conception and design: Daniel P. Petrylak, Nobuaki Matsubara, Andrew J. Armstrong, Winald Gerritsen, Charles Schloss, Christian H. Poehlein, Karim Fizazi
Financial support: Christian H. Poehlein
Administrative support: Christian H. Poehlein
Provision of study materials or patients: Nobuaki Matsubara, Ernesto Korbenfeld, Rustem Gafanov, Loic Mourey, Tilman Todenhöfer, Howard Gurney, Gero Kramer, Andries M. Bergman, Andrew J. Armstrong, Winald Gerritsen, Ray McDermott, Sergio Bracarda, Ray Manneh, Christian H. Poehlein, Karim Fizazi
Collection and assembly of data: Daniel P. Petrylak, Raffaele Ratta, Nobuaki Matsubara, Ernesto Korbenfeld, Rustem Gafanov, Loic Mourey, Tilman Todenhöfer, Howard Gurney, Gero Kramer, Andries M. Bergman, Pawel Zalewski, Maria De Santis, Andrew J. Armstrong, Winald Gerritsen, Russell Pachynski, Seok Soo Byun, Eric Levesque, Ray McDermott, Sergio Bracarda, Ray Manneh, Meital Levartovsky, Charles Schloss, Christian H. Poehlein, Karim Fizazi
Data analysis and interpretation: Daniel P. Petrylak, Raffaele Ratta, Nobuaki Matsubara, Ernesto Korbenfeld, Rustem Gafanov, Andries M. Bergman, Pawel Zalewski, Maria De Santis, Andrew J. Armstrong, Winald Gerritsen, Seok Soo Byun, Margitta Retz, Eric Levesque, Ray McDermott, Ray Manneh, Xin Tong Li, Charles Schloss, Christian H. Poehlein, Karim Fizazi
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The authors thank the participants and their families and caregivers, all primary investigators and their site personnel; Joseph E. Burgents of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Rahway, NJ (MSD), for study design support; Bethanne Friedman, Christina Canales, and Tevea Kem of MSD for study support; Haiyan Wu and Christine K. Gause of MSD for statistical support; Scot W. Ebbinghaus and Kentaro Imai of MSD for study support and critical review; and Ina Nikolaeva of MSD for medical writing assistance. List of study sites, investigators, and number of participants are provided in Appendix Table A1 (online only).

REFERENCES

1. Parker C, Castro E, Fizazi K, et al: Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 31:1119-1134, 2020
2. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Prostate cancer (version 1.2025). https://www.nccn.org
3. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-1512, 2004
4. Petrylak DP, Tangen CM, Hussain MH, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 351:1513-1520, 2004
5. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet 376:1147-1154, 2010
6. de Wit R, de Bono J, Sternberg CN, et al: Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 381:2506-2518, 2019
7. Petrylak DP, Vogelzang NJ, Budnik N, et al: Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 16:417-425, 2015
8. Araujo JC, Trudel GC, Saad F, et al: Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): A randomised, double-blind phase 3 trial. Lancet Oncol 14:1307-1316, 2013
9. Fizazi K, Higano CS, Nelson JB, et al: Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 31:1740-1747, 2013
10. Scher HI, Jia X, Chi K, et al: Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. J Clin Oncol 29:2191-2198, 2011

11. Tannock IF, Fizazi K, Ivanov S, et al: Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): A phase 3, double-blind randomised trial. Lancet Oncol 14:760-768, 2013
12. Chi KN, Higano CS, Blumenstein B, et al: Custirsen in combination with docetaxel and prednisone for patients with metastatic castration-resistant prostate cancer (SYNERGY trial): A phase 3, multicentre, open-label, randomised trial. Lancet Oncol 18:473-485, 2017
13. Quinn DI, Tangen CM, Hussain M, et al: Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): A randomised phase 3 trial. Lancet Oncol 14:893-900, 2013
14. Petrylak DP, Loriot Y, Shaffer DR, et al: Safety and clinical activity of atezolizumab in patients with metastatic castration-resistant prostate cancer: A phase I study. Clin Cancer Res 27:3360-3369, 2021
15. Fizazi K, Gonzalez Mella P, Castellano D, et al: Nivolumab plus docetaxel in patients with chemotherapy-naive metastatic castration-resistant prostate cancer: Results from the phase II CheckMate 9KD trial. Eur J Cancer 160:61-71, 2022
16. Antonarakis ES, Piulats JM, Gross-Goupil M, et al: Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: Multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 38:395-405, 2020
17. Yu EY, Kolinsky MP, Berry WR, et al: Pembrolizumab plus docetaxel and prednisone in patients with metastatic castration-resistant prostate cancer: Long-term results from the phase 1b/2 KEYNOTE-365 cohort B study. Eur Urol 82:22-30, 2022
18. Sfanos KS, Bruno TC, Maris CH, et al: Phenotypic analysis of prostate-infiltrating lymphocytes reveals TH17 and Treg skewing. Clin Cancer Res 14:3254-3261, 2008
19. Jayaprakash P, Ai M, Liu A, et al: Targeted hypoxia reduction restores T cell infiltration and sensitizes prostate cancer to immunotherapy. J Clin Invest 128:5137-5149, 2018
20. de Bono JS, Smith MR, Saad F, et al: Subsequent chemotherapy and treatment patterns after abiraterone acetate in patients with metastatic castration-resistant prostate cancer: Post hoc analysis of COU-AA-302. Eur Urol 71:656-664, 2017
21. Shore ND, Ionescu-Ittu R, Laliberte F, et al: Beyond frontline therapy with abiraterone and enzalutamide in metastatic castration-resistant prostate cancer: A real-world US study. Clin Genitourin Cancer 19:480-490, 2021
22. Gevensleben H, Dietrich D, Golletz C, et al: The immune checkpoint regulator PD-L1 is highly expressed in aggressive primary prostate cancer. Clin Cancer Res 22:1969-1977, 2016
23. Cristescu R, Aurora-Garg D, Albright A, et al: Tumor mutational burden predicts the efficacy of pembrolizumab monotherapy: A pan-tumor retrospective analysis of participants with advanced solid tumors. J Immunother Cancer 10:e003091, 2022
24. Maio M, Ascierto PA, Manzyuk L, et al: Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: Updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 33:929-938, 2022
25. Rebuzzi SE, Rescigno P, Catalano F, et al: Immune checkpoint inhibitors in advanced prostate cancer: Current data and future perspectives. Cancers (Basel) 14:1245, 2022
26. George DJ, Sartor O, Miller K, et al: Treatment patterns and outcomes in patients with metastatic castration-resistant prostate cancer in a real-world clinical practice setting in the United States. Clin Genitourin Cancer 18:284-294, 2020
27. Chowdhury S, Bjartell A, Lumen N, et al: Real-world outcomes in first-line treatment of metastatic castration-resistant prostate cancer: The prostate cancer registry. Target Oncol 15:301-315, 2020
28. Verry C, Vincendeau S, Massetti M, et al: Pattern of clinical progression until metastatic castration-resistant prostate cancer: An epidemiological study from the European prostate cancer registry. Target Oncol 17:441-451, 2022
29. Gillessen S, Bossi A, Davis ID, et al: Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. Eur J Cancer 185:178-215, 2023

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pembrolizumab Plus Docetaxel Versus Docetaxel for Previously Treated Metastatic Castration-Resistant Prostate Cancer: The Randomized, Double-Blind, Phase III KEYNOTE-921 Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Daniel P. Petrylak
Consulting or Advisory Role: Bayer, Exelixis, Pfizer, Roche, Astellas Pharma, AstraZeneca, Lilly, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Incyte, Janssen, Pharmacyclics, Seagen, Urogen Pharma, Advanced Accelerator Applications, Ipsen, Bicycle Therapeutics, Mirati Therapeutics, Monopteros Therapeutics, Regeneron, Gilead Sciences
Research Funding: Progenics (Inst), Sanofi (Inst), Endocyte (Inst), Genentech (Inst), Merck (Inst), Astellas Medivation (Inst), Novartis (Inst), AstraZeneca (Inst), Bayer (Inst), Lilly (Inst), Innocrin Pharma (Inst), MedImmune (Inst), Pfizer (Inst), Roche (Inst), Seagen (Inst), Clovis Oncology (Inst), Bristol Myers Squibb (Inst), Advanced Accelerator Applications (Inst), Agensys (Inst), BioXCel therapeutics (Inst), Eisai (Inst), Mirati Therapeutics (Inst), Replimune (Inst), Medivation (Inst), Gilead Sciences (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Expert Testimony: Celgene, Sanofi

Raffaele Ratta
Honoraria: Ipsen, MSD Oncology, AstraZeneca, Bristol Myers Squibb, Pfizer, Advanced Accelerator Applications, Eisai
Consulting or Advisory Role: Astellas Pharma, Pfizer, Ipsen, MSD
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Ipsen, MSD Oncology, Janssen

Nobuaki Matsubara
Honoraria: Sanofi
Consulting or Advisory Role: Sanofi, Janssen, AstraZeneca, Lilly, Amgen, Seagen, Pfizer
Research Funding: Janssen (Inst), MSD (Inst), Bayer Yakuhin (Inst), Chugai Pharma (Inst), AstraZeneca (Inst), Astellas Pharma (Inst), Bayer (Inst), Amgen (Inst), Takeda (Inst), Lilly (Inst), Eisai (Inst), Roche/Genentech (Inst), Seagen (Inst), Novartis (Inst), AbbVie (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Ernesto Korbenfeld
Honoraria: AstraZeneca
Consulting or Advisory Role: Pfizer
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Rustem Gafanov
Honoraria: Janssen, Astellas Pharma, Bayer, Sanofi, MSD, Bristol Myers Squibb, Pfizer
Consulting or Advisory Role: Janssen, Astellas Pharma, Bayer, Sanofi, MSD, Bristol Myers Squibb, Pfizer
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Speakers' Bureau: Janssen, Astellas Pharma, Bayer, Sanofi, MSD, Bristol Myers Squibb, Pfizer

Loic Mourey
Honoraria: Sanofi, Astellas Pharma, Janssen, Pfizer, Ipsen, Bristol Myers Squibb, AstraZeneca, Advanced Accelerator Applications, Eisai, MSD
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Sanofi, Astellas Pharma, Janssen, Pfizer, AstraZeneca, BMS, Ipsen, Advanced Accelerator Applications, Eisai, MSD

Tilman Todenhöfer
Consulting or Advisory Role: Astellas Pharma, Amgen, AstraZeneca/Merck, Bayer, Bristol Myers Squibb/Sanofi, Janssen, Merck Serono, MSD Oncology, Pfizer, Roche, Sanofi/Aventis, Lilly
Research Funding: Astellas Pharma (Inst), Bayer (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc (Inst), Lilly (Inst), Pfizer (Inst), AstraZeneca/MedImmune (Inst), RhoVac (Inst), Immunomedics (Inst), Basilea (Inst), Janssen (Inst)

Howard Gurney
Consulting or Advisory Role: Bristol Myers Squibb, Ipsen, Merck Sharp & Dohme, AstraZeneca, Janssen-Cilag, Pfizer, Roche, Merck Serono, Astellas Pharma
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Speakers' Bureau: Merck Serono, AstraZeneca, Ipsen

Gero Kramer
Consulting or Advisory Role: Janssen, AstraZeneca, MSD Life Science Foundation, Bayer, Ferring, Astellas Pharma, BMS, Accord Healthcare, Ipsen, Novartis, Pfizer
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Bayer, Janssen, Astellas Pharma, MSD

Andries M. Bergman
Consulting or Advisory Role: Sanofi, Bayer, Janssen, Astellas Pharma
Research Funding: Bayer, Astellas Pharma, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Bayer

Pawel Zalewski
Consulting or Advisory Role: Ipsen, BMS, Merck, AstraZeneca, Novartis, Pfizer
Research Funding: Merck, BMS, Clovis Oncology, Seagen, Gilead Sciences, AstraZeneca, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Maria De Santis
Honoraria: Roche/Genentech, Bayer, Novartis, Astellas Pharma, Immunomedics, Amgen, Janssen-Cilag, Ipsen, MSD Oncology, Merck Serono, Merck Sharp & Dohme, Pfizer, Sandoz-Novartis, Basilea, BioClin Therapeutics, Orion, Bristol Myers Squibb, Seagen, Ferring, Sanofi, AstraZeneca/MedImmune, Gilead Sciences, AAA HealthCare, Accord Healthcare, Exelixis/Ipsen, Thermosome
Consulting or Advisory Role: Roche/Genentech, Ipsen, Astellas Pharma, Janssen, GlaxoSmithKline, Takeda, Bristol Myers Squibb, Merck Sharp & Dohme, Bayer, Sanofi, Ferring, Basilea, BioClin Therapeutics, AstraZeneca, BioSyn Healthy Pharma, Sandoz-Novartis, Amgen, Seagen, AAA HealthCare, Accord Healthcare, Novartis, Gilead Sciences, Orion Health, Johnson & Johnson/Janssen, Immunomedics/Gilead, Eisai, Thermosome
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Sanofi, Bayer, Janssen, Ipsen, Roche, Astellas Pharma, Bristol Myers Squibb, Merck Serono, Roche/Genentech, AstraZeneca, Pfizer, Eisai

Andrew J. Armstrong
Consulting or Advisory Role: Bayer, Pfizer, Astellas Scientific and Medical Affairs Inc, AstraZeneca, Merck, Bristol Myers Squibb, Janssen, Novartis, Exelixis, Myovant Sciences, GoodRx, Cytogen
Research Funding: Bayer (Inst), Pfizer (Inst), Novartis (Inst), Janssen Oncology (Inst), Astellas Pharma (Inst), Bristol Myers Squibb (Inst), Merck (Inst), AstraZeneca (Inst), Amgen (Inst), Syntrix Biosystems (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Patents, Royalties, Other Intellectual Property: Circulating tumor cell novel capture technology (Inst)
Travel, Accommodations, Expenses: Astellas Scientific and Medical Affairs Inc

Winald Gerritsen
Consulting or Advisory Role: Novartis, Coretag, ORCA Therapeutics, MSD Oncology, Bayer
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Expert Testimony: Astellas Medivation

Russell Pachynski
Stock and Other Ownership Interests: Pixie Biosciences, Inc
Consulting or Advisory Role: Bristol Myers Squibb, Pfizer/EMD Serono, Sanofi, Dendreon, Bayer, Blue Earth Diagnostics, Tolmar Therapeutics, Janssen Oncology, Eisai, Exelixis, Macrogenics
Speakers' Bureau: Merck, Bayer
Research Funding: Janssen Oncology, Pharmacyclics (Inst), Bristol Myers Squibb Foundation (Inst), Exelixis (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Patents, Royalties, Other Intellectual Property: Titled: Method of cell-free DNA analysis to identify high-risk metastatic prostate cancer, Compositions comprising chemerin and methods of use thereof
Travel, Accommodations, Expenses: Genentech/Roche

Seok Soo Byun
Employment: Invietes Biocore, Invites Genomics
Leadership: Invites Biocore, Invites Genomics
Stock and Other Ownership Interests: Procagen, CG Invites
Honoraria: AstraZeneca
Research Funding: AstraZeneca, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Janssen Oncology, Astellas Pharma, Pfizer

Margitta Retz
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Eric Levesque
Honoraria: Bayer, AstraZeneca
Consulting or Advisory Role: Novartis
Research Funding: Merck (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Ray McDermott
Honoraria: Bayer, Sanofi, Janssen, Astellas Pharma, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Novartis, Clovis Oncology, Ipsen
Speakers' Bureau: MSD Oncology
Research Funding: Sanofi (Inst), Janssen (Inst), Bayer (Inst), Astellas Pharma (Inst), Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Pfizer, Janssen-Cilag, Roche, Ipsen

Sergio Bracarda
Consulting or Advisory Role: Genenta Science, Indicon
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: MSD Oncology, Pfizer, Merck Serono, Bayer Schering Pharma, Ipsen

Ray Manneh
Leadership: Sociedad de Oncología y Hematología del Cesar (I)
Honoraria: Astellas Scientific and Medical Affairs Inc, Janssen-Cilag, Bayer, Merck Sharp & Dohme, Roche, Bristol Myers Squibb, Sanofi, AstraZeneca, Pfizer, Lilly, Ipsen, Amgen, Merck Serono, Novartis, Tecnofarma
Consulting or Advisory Role: Astellas Pharma, Janssen-Cilag, Roche, Merck Serono, Merck Sharp & Dohme, AstraZeneca, Sanofi, Pfizer, Bayer, Ipsen, Tecnofarma
Speakers' Bureau: San Jorge Foundation, Asociación Colombiana de Hematoligía y Oncología (ACHO)
Research Funding: Pfizer, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc, Novartis, Amgen, Bristol Myers Squibb/Celgene
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Roche/Genentech, Pfizer, Bayer

Meital Levartovsky
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Xin Tong Li
Employment: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Charles Schloss
Employment: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Stock and Other Ownership Interests: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Christian H. Poehlein
Employment: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Leadership: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Stock and Other Ownership Interests: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc

Karim Fizazi
Honoraria: Janssen (Inst), Astellas Pharma (Inst), Bayer (Inst), Novartis (Inst)
Consulting or Advisory Role: Janssen Oncology (Inst), Bayer (Inst), Astellas Pharma (Inst), Sanofi (Inst), Orion, AstraZeneca (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Clovis Oncology (Inst), Novartis (Inst), Pfizer (Inst), Daiichi Sankyo Europe GmbH (Inst), MSD (Inst)
Research Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc
Travel, Accommodations, Expenses: Janssen, MSD, AstraZeneca, Pfizer, Bayer

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. List of Study Sites, Investigators, and Number of Participants Randomly Assigned to the Study (continued)

Site Location	Principal Investigator[a]
China	Weiqing Han/Shusuan Jiang Hongqian Guo Zhisong He Dingwei Ye Jian Huang Jinchun Xing Shaozhong Wei Yongda Liu Dexin Yu Jianming Guo Yong Yang Qi Zhang Chaohong He Fangjian Zhou Dalin He Lulin Ma Lijun Chen Wei Chen Jimin Chen Hao Zeng Hui Chen Wei Xue Yonglian Guo Wanlong Tan
Colombia	Ray Manneh Kopp Jesus Sanchez Castillo Gustavo Rojas-Uribe Daniel Rojas Castillo/Laura Bernal Vaca Fernando Oviedo Martinez Alvaro Gomez Diaz/Carolina Lopez Carlos Morales Carmen Alcala Castro Jose Correa Oscar Madiedo
France	Raffaele Ratta Loic Mourey Werner Hilgers Denis Maillet Gwenaelle Gravis Guilhem Roubaud Karim Fizazi Hakim Mahammedi Benjamin Auberger Emmanuelle Bompas Antoine Thiery-Vuillemin/Maurina Tristan Aude Flechon Dominique Spaeth Aline Houessinon Mostefa Bennamoun Jerome Meunier/Heba Dawood/Elise Champeaux Orange Mohamad Chehimi Louis-Marie Dourthe
Germany	Tilman Todenhöfer Maria de Santis Arnulf Stenzl Margitta Retz Christian Gratzke Philipp Nuhn Georgios Gakis Julius Van Essen/Matthias Saar Marinela Augustin Arne Strauss Julia Heinzelbecker Marc-Oliver Grimm

(continued in next column)

TABLE A1. List of Study Sites, Investigators, and Number of Participants Randomly Assigned to the Study

Site Location	Principal Investigator[a]
Argentina	Ignacio Alfredo Casarini Nicolas Castagneris Alejandro Dri Felipe Palazzo Andrea Marchioni Diego Kaen Ernesto Korbenfeld Mauricio Fernandez Lazzaro Juan Ignacio Hernandez Moran Aldo Perfetti Juan Pablo Sade Margarita Sonia Alfie Andrea Marchioni Mirta S. Varela Jorge Emilio Salinas Juan Zarba
Australia	Rohit Joshi Ian Davis David Pook Girish Mallesara Wade Pullin Howard Gurney Stephen Donald Begbie Thean Hsiang Tan Jeffrey Goh Patricia Bastick Emma Beardsley Daniel Brungs Kieron Bigby Thomas Ferguson Siobhan Ng David Martin
Austria	Richard Greil Isabel Heidegger Pircher Wolfgang Loidl/Ferdinand Luger Thomas Bauernhofer Gero Kramer
Brazil	Andre Poisl Fay Jose Augusto Rinck Junior Giuliano Borges Luiza Aleixo Barros Leite Ferreira Fabio Franke
Canada	Pawel Zalewski Eric Levesque Michel Pavic Urban Emmenegger/Martin Smoragiewicz Gabrielle Gagnon Aaron Hansen/Adrian Sacher/Di Maria Jiang Aly-Khan Lalani Robyn Macfarlane Andrea Molckovsky
Chile	Osvaldo Aren/Mauricio Burotto Patricio Yanez Weber Eugenia Loredo Fort Mauricio Mahave Felipe Rey Carolina Ibanez

(continued on following page)

TABLE A1. List of Study Sites, Investigators, and Number of Participants Randomly Assigned to the Study (continued)

Site Location	Principal Investigator[a]
Ireland	Ray McDermott Richard Bambury Thamir Mahgoub/Grzegorz Korpanty
Israel	Meital Levartovsky Avivit Peer Eli Rosenbaum/Daniel Goldstein Stephen Jay Frank David Sarid Igal Kushnir Avishay Sella Keren Rouvinov
Italy	Sergio Bracarda Paolo Zucali Gaetano Facchini/Sandro Pignata Giuseppe Banna/Giuseppa Scandurra Roberto Sabbatini Orazio Caffo Fabio Calabro/Linda Cerbone
Japan	Nobuaki Matsubara Takeo Kosaka Motohide Uemura/Kouji Hatano Hiroji Uemura Hideaki Miyake Kenichi Tabata/Hideyasu Tsumura Masaki Shiota Koshiro Nishimoto /Kento Kanao Kouji Izumi Gaku Arai/Kazutaka Saito Nobumichi Tanaka Hiroyoshi Suzuki Satoshi Fukasawa/Atsushi Komaru Go Kimura Yuji Miura Masafumi Matsumura/Katsuyoshi Hashine Yoshiaki Yamamoto/Hiroaki Matsumoto/Koji Shiraishi Hideki Sakai/Yasuyoshi Miyata/Kensuke Mitsunari Hirotsugu Uemura Naoki Terada/Toshiyuki Kamoto
The Netherlands	Andries M. Bergman Winald Gerritsen/Niven Mehra Marco Ben Polee Irma Oving Pieter Van Den Berg Arnold Baars Danny Houtsma Laurence Van Warmerdam Addy Luijtgaarden Yes Van De Wouw Tineke Smilde
Russian Federation	Rustem Gafanov Andrey Novikov Ruslan Zukov Sergey Mishugin Boris Alekseev Evgeniy Kopyltsov Dmitry Nosov Natalia Fadeeva Sergey Alekseev Petr Karlov Michail Shkolnik Anna Tarasova Sergey Afanasyev

(continued in next column)

TABLE A1. List of Study Sites, Investigators, and Number of Participants Randomly Assigned to the Study (continued)

Site Location	Principal Investigator[a]
South Korea	Seok Soo Byun Jae Young Joung Cheol Kwak Bumjin Lim Seong Soo Jeon
Spain	Begona Mellado Gonzalez Javier Puente Vazquez Javier Molina Cerrillo Begona Perez Valderrama Josep Piulats Rodriguez Alejo Rodriguez-Vida Nuria Sala Gonzalez Ignacio Duran Martinez Juan Rodriguez Moreno Enrique Gallardo Diaz Maria Isabel Saez Medina
Taiwan	Kun-Yuan Chiu/Chia-Yen Lin Chao-Hsiang Chang Yi-Hsiu Huang Yu-Chieh Tsai Wen-Pin Su
United Kingdom	Peter Hoskin Danish Mazhar Jorg Michels/Anna Lydon Johann S. De Bono Salil Vengalil Thomas Powles Amit Bahl Carmel Pezaro
United States	Russell Pachynski Thomas Flaig Sreenivasa Chandana Vagif Atduev Andrew J. Armstrong Lawrence Fong Daniel Petrylak Michael Goodman Jeanny Aragon-Ching Tomasz M. Beer/Julie Graff Julie Kish Mark Kochenderfer Robert Alter Clara Hwang Prateek Mendiratta William Eyre Lawler/Giribala Patel Patrick Cobb Jigarkumar Parikh Ralph Hauke Mohammed Kassem Neal Shore Bharat Barai Will Voelzke Christopher Pieczonka David Quinn Moh'd Khushman Ulka Vaishampayan Nicholas Vogelzang

[a]If the original investigator has been replaced, that investigator's name is followed by a slash (/) and the replacement investigator's name.