

Brief Report

Pembrolizumab Plus Lenvatinib in Participants with Docetaxel-pretreated Metastatic Castration-resistant Prostate Cancer: Results from KEYNOTE-365 Cohort E

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Abstract

Pembrolizumab has shown manageable safety and modest antitumor activity when used as a single agent in participants with metastatic castration-resistant prostate cancer (mCRPC). Preclinical evidence suggests that lenvatinib, a vascular endothelial growth factor-targeted agent, inhibits angiogenesis and cell migration in prostate cancer. Safety and efficacy of pembrolizumab plus lenvatinib in participants with docetaxel-pretreated mCRPC were evaluated in cohort E of the phase 1b/2 KEYNOTE-365 study. Eligible adults with confirmed mCRPC, Eastern Cooperative Oncology Group performance status (ECOG PS) scores of 0 or 1, and prior docetaxel treatment for mCRPC received pembrolizumab 200 mg intravenously every 3 wk, for ≤ 35 cycles, plus oral lenvatinib 20 mg daily, continuously from day 1 of cycle 1, unless specific discontinuation criteria were met. Primary endpoints were prostate-specific antigen (PSA) response rate; objective response rate (ORR), per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) v1.1, by blinded independent central review; and safety. A total of 39 participants received treatment, with a median follow-up of 9.7 mo (interquartile range, 8.5–11.3). Confirmed PSA response rate was 34% (95% confidence interval [CI], 20–51).

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Lenvatinib
Metastatic castration-resistant
prostate cancer
Pembrolizumab

ORR for participants with RECIST-measurable disease was 36% (95% CI, 18–57). Treatment-related adverse events (AEs) of any grade occurred in 92% of participants and grade 3–5 treatment-related AEs occurred in 62% of participants. Two participants died of non-treatment-related AEs (acute kidney injury and unspecified death).

Clinical trial registry: NCT02861573.

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ADVANCING PRACTICE

What Does This Study Add?

This study demonstrates antitumor activity of immune-targeted combination therapy, pembrolizumab and lenvatinib, in participants with metastatic castration-resistant prostate cancer (mCRPC) who received prior chemotherapy. An objective response was observed in 36% of participants with measurable disease, and the confirmed prostate-specific antigen (PSA) response rate was 34%. Additional research is warranted to identify the select population that would derive the greatest benefit from this combination therapy.

Clinical Relevance

This study shows that pembrolizumab plus lenvatinib has measurable antitumor activity in docetaxel-pretreated mCRPC, with a confirmed PSA response rate of 34% and an objective response rate of 36% in participants with measurable disease. Responses were observed across PD-L1 subgroups, including 12 PD-L1-positive, 14 PD-L1-negative, and 12 participants with unknown status, with no clear enrichment by PD-L1 expression. Treatment-related adverse events were frequent, with grade 3–5 events observed in 62% of participants. These were consistent with the known profiles of both agents. These findings support further evaluation of this immunotherapy–antiangiogenic combination but also highlight the need to identify patients most likely to benefit. *Associate Editor: Elena Castro.*

Patient Summary

In participants with castration-resistant prostate cancer that has spread from where it started and who were previously treated with chemotherapy, combination of pembrolizumab (a drug that treats certain cancers by helping the immune system) with lenvatinib (a drug that stops cancers developing new blood vessels) showed antitumor activity, with a safety profile consistent with previous studies.

Treatment guidelines for metastatic castration-resistant prostate cancer (mCRPC) include combining continued androgen deprivation therapy (ADT) with docetaxel or the androgen receptor pathway inhibitors (ARPIs), abiraterone, or enzalutamide; however, many patients experience disease progression [1]. Agents such as cabazitaxel, lutetium-177-PSMA-617, Poly (ADP-ribose) polymerase inhibitors, and radium-223, in combination with continued ADT, are available after treatment with docetaxel and ARPI therapy; however, more effective therapies that prolong survival are needed [1].

Vascular endothelial growth factors and their receptors, associated with angiogenesis and growth and metastasis of tumor cells, have been shown to be overexpressed in prostate cancer [2]. Targeting these pro-angiogenic mechanisms has been of interest in the development of novel treatment options for prostate cancer [3]. Antiangiogenic agents, such as sunitinib and cabozantinib, have shown some antitumor activity in clinical trials, and preclinical evidence suggests that the multitargeted kinase inhibitor lenvatinib inhibits cell proliferation and angiogenesis in prostate cancer [4–6]. The immunomodulatory effect of lenvatinib complements that of checkpoint inhibition and may result in a potent combination effect with pembrolizumab,

a programmed cell death protein-1 (PD-1) inhibitor. This combination has shown durable efficacy in renal cell carcinoma [7].

Here, we present results from cohort E of the phase 1b/2 KEYNOTE-365 study (NCT02861573), which evaluated the efficacy and safety of pembrolizumab plus lenvatinib in participants with docetaxel-pretreated mCRPC.

Men aged ≥ 18 yr with histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology, and disease progression ≤ 6 mo from screening (by prostate-specific antigen [PSA] progression or radiographic soft tissue/bone progression), were eligible. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent.

Participants received pembrolizumab 200 mg intravenously every 3 wk (≤ 35 cycles) plus oral lenvatinib 20 mg capsules daily, until disease progression, unacceptable toxicity, or withdrawal.

The primary endpoints were PSA response rate; objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by blinded independent central review (BICR); and safety and tolerability. Sec-

ondary endpoints were time to PSA progression, ORR, and radiographic progression-free survival (rPFS) per Prostate Cancer Working Group 3 (PCWG3)–modified RECIST v1.1, by BICR; overall survival (OS); duration of response (DOR); and disease control rate (DCR) per RECIST v1.1 and PCWG3–modified RECIST v1.1 by BICR. For DOR, participants were censored at the time of last adequate assessment, progressive disease, or death. For time to PSA progression and rPFS, participants were censored at the last assessment. For OS, participants were censored at the last date they were known to be alive; those without survival data were censored at day 1.

Additional eligibility criteria, endpoint definitions, additional efficacy and safety assessment information, and statistical analyses are provided in the supplement.

Between October 20, 2021, and August 5, 2022, 40 participants were enrolled, and 39 of them received treatment. The median age was 67.0 yr (interquartile range [IQR], 63–72), and 12 participants (31%) had programmed cell death-ligand 1 (PD-L1)–positive tumors ([Supplementary Table 1](#)). Median time from first dose to database cutoff was 9.7 mo (IQR, 8.5–11.3). As of January 25, 2023, 25 participants (64%) discontinued treatment; reasons for discontinuation were progressive disease ($n = 12$, 31%), adverse events (AEs) ($n = 7$, 18%), clinical progression ($n = 5$, 13%), and lost to follow-up ($n = 1$, 2.6%) ([Supplementary Fig. 1](#)). Median duration of all therapies was 6.5 mo (IQR, 2.9–8.1).

Confirmed PSA response rates among participants with baseline PSA measurements ($n = 38$) were 34% (13/38) in the total population, 33% (4/12) in participants with PD-L1–positive disease, and 43% (6/14) in participants with PD-L1–negative disease (12 participants [32%] had unknown PD-L1 status). Thirty-one of 38 participants (82%) had any reduction in PSA from baseline, and 20 participants (53%) had $\geq 50\%$ PSA reduction from baseline ([Fig. 1A](#)). Median time to confirmed PSA progression was 4.6 mo (IQR, 3.4–not reached [NR]; [Supplementary Fig. 2](#)). PSA response rate by subgroup is presented in [Supplementary Fig. 3A](#).

Confirmed ORR per RECIST v1.1 by BICR for participants with measurable disease (25/39) was 36% (95% confidence interval [CI], 18–57; 9 partial responses [PRs]) and DCR was 56% (95% CI, 35–76; [Table 1](#)). Median DOR was NR (IQR, 6.1–NR), and 3 participants had responses lasting ≥ 6 mo. ORR by subgroup is presented in [Supplementary Fig. 3B](#). Of the 6 participants with liver metastases at baseline, 2 had stable disease and 4 developed progressive disease per RECIST v1.1 by BICR. DCR by subgroup is presented in [Supplementary Fig. 3C](#).

Per PCWG3–modified RECIST v1.1 by BICR, confirmed ORR was 36% (95% CI, 18–57) for participants with measurable disease ([Supplementary Table 2](#)). In all treated participants, DCR was 51% (95% CI, 35–68). Median DOR was NR (IQR, 6.1–NR), and 3 participants had responses lasting ≥ 6 mo.

In all treated participants, median rPFS was 7.9 mo (95% CI, 4.1–NR); the 6-mo rPFS rate was 64%; and the 12-mo rPFS rate was 35% ([Fig. 1B](#)). Median rPFS was 6.4 mo (95% CI, 2.0–NR) in participants with PD-L1–positive mCRPC;

NR (95% CI, 2.1–NR) in participants with PD-L1–negative mCRPC; and 7.9 mo (95% CI, 3.6–NR) in participants with unknown PD-L1 status ([Supplementary Fig. 4A](#)). Median rPFS by subgroup is presented in [Supplementary Table 3](#). Median OS was 9.4 mo (95% CI, 8.4–NR); 6-mo OS rate was 77%; and 12-mo OS rate was 37% ([Fig. 1C](#)). Median OS was 9.4 mo (95% CI, 4.9–NR) in participants with PD-L1–positive mCRPC; NR (95% CI, 3.2–NR) in participants with PD-L1 negative mCRPC; and 8.7 mo (95% CI, 4.1–NR) in participants with unknown PD-L1 status ([Supplementary Fig. 4B](#) and [Supplementary Table 3](#)). Median OS by subgroup is presented in [Supplementary Table 3](#).

Treatment-related AEs occurred in 36 participants (92%) ([Supplementary Table 4](#)). Grade 3–4 treatment-related AEs occurred in 24 participants (62%). Treatment was interrupted in 28 participants (72%) because of treatment-related AEs. Pembrolizumab-related AEs resulted in treatment interruption in 16 participants (41%), and lenvatinib-related AEs resulted in interruption in 27 participants (69%). At least one study drug was discontinued in 11 participants (28%) because of treatment-related AEs ([Supplementary Table 5](#)). Pembrolizumab was discontinued in 5 participants (13%) and lenvatinib was discontinued in nine (23%). Two participants (5%) died due to all-cause AEs (acute kidney injury and unspecified death) that were not considered treatment related. AEs of clinical interest associated with lenvatinib occurred in 34 participants (87%), and 21 participants (54%) experienced grade 3–5 AEs ([Supplementary Table 6](#)). Immune-mediated AEs and infusion reactions occurred in 25 participants (64%), and 2 participants (5%) experienced grade 3 AEs ([Supplementary Table 7](#)).

In this study, pembrolizumab plus lenvatinib demonstrated antitumor activity in participants with docetaxel-pretreated mCRPC. Results were consistent with the modest activity observed in other studies of PD-1 inhibitors as monotherapy or combination therapy in docetaxel-pretreated mCRPC (ORR, 5–15%) [8,9], which may be due to PD-(L)1-mediated tumor immune escape mechanisms [10]. However, sample sizes in this study were small, and the results should be interpreted with caution. The safety of pembrolizumab plus lenvatinib was generally consistent with the known profiles of the individual agents and of the combination [11,12].

Limitations of this study included the small sample size of both the overall population, as well as the subgroups, which limits interpretability, and the lack of a comparator group, preventing direct comparison. Additionally, PD-L1 status was unknown in 1/3 of participants, and the results should be interpreted with caution.

In conclusion, pembrolizumab plus lenvatinib exhibits antitumor activity in participants with docetaxel-pretreated mCRPC. Future research may identify the select population that would benefit from this combination therapy.

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

Study concept and design: Kose, Imai.

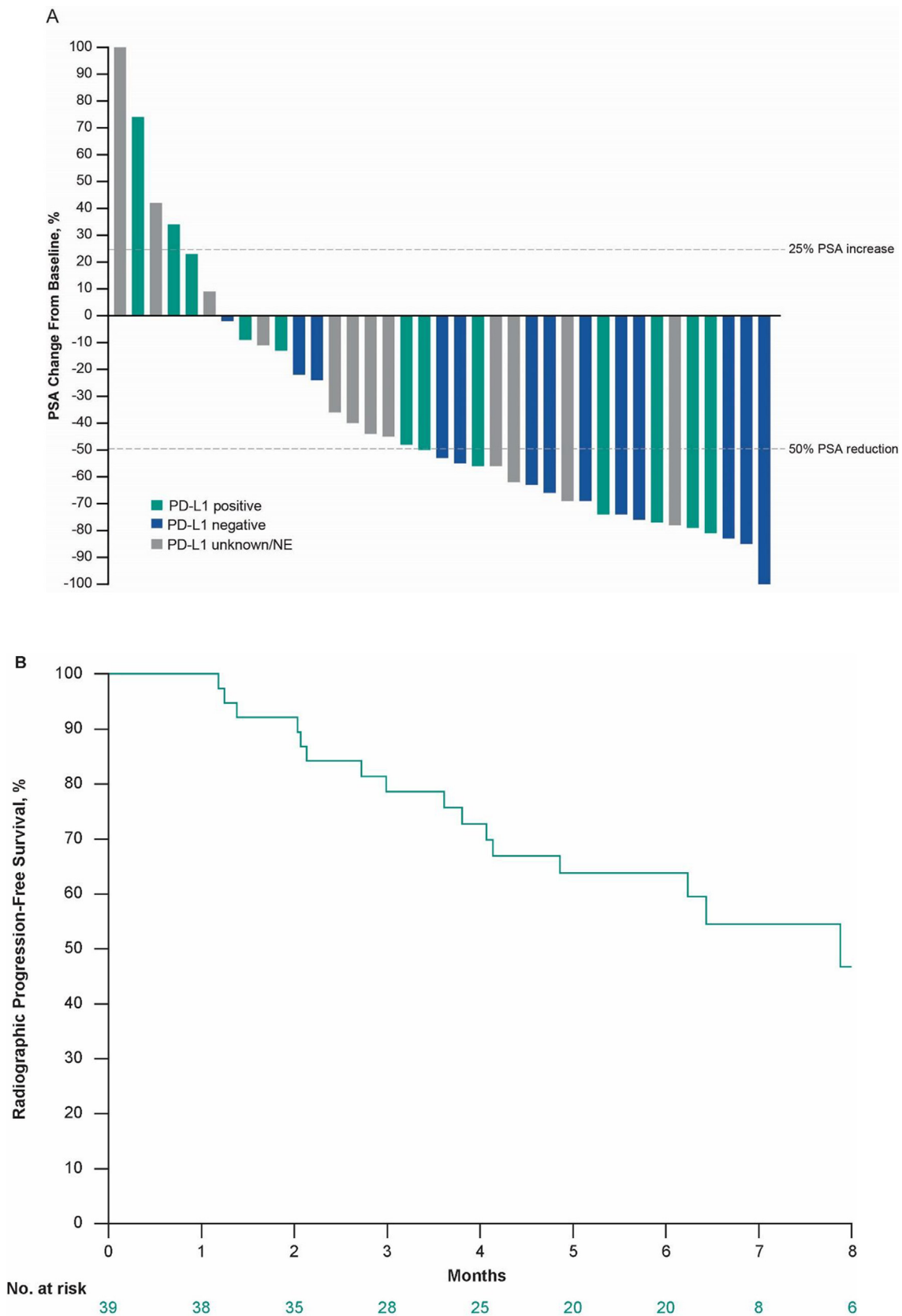


Fig. 1 – (A) PSA percentage change from baseline (confirmed and unconfirmed) by PD-L1 status ^a, (B) Kaplan-Meier estimates of rPFS per PCWG3-modified RECIST v1.1, and (C) Kaplan-Meier estimates of OS. NE = not evaluable; NR = not reached; OS = overall survival; PCWG-3 = Prostate Cancer Clinical Trials Working Group 3; PD-L1 = programmed cell death-ligand 1; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; RECIST v1.1 = Response Evaluation Criteria for Solid Tumors, version 1.1. ^a Bars include 37 participants with baseline and postbaseline PSA assessments.

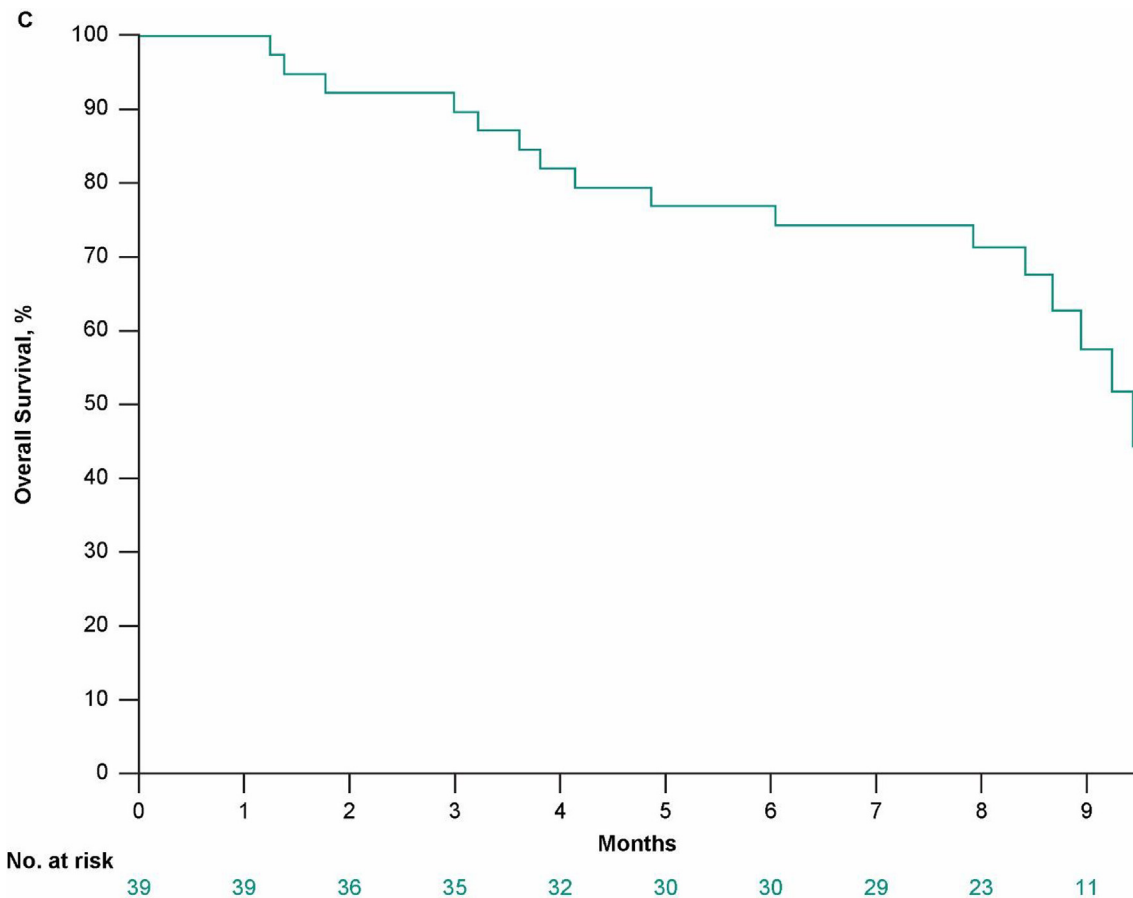


Fig. 1 (continued)

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

RECIST-measurable disease (n = 25)	
ORR ^a , n (%) [95% CI]	9 (36 [18–57])
DCR ^b , n (%) [95% CI]	14 (56 [35–76])
Best response, n (%)	
CR	0
PR	9 (36)
SD of any duration	8 (32)
Non-CR/non-PD	0
SD or non-CR/non-PD ≥6 mo	5 (20)
PD	5 (20)
No assessment ^c	3 (12)
DOR ^d , median (IQR), mo	NR (6.1–NR)

BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; IQR = interquartile range; NR = not reached; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria for Solid Tumors, version 1.1; SD = stable disease.

^a Based on binomial exact CI method.

^b Defined as the proportion of participants who had an objective response (CR or PR) of any duration or who had SD or non-CR/non-PD for at least 6 mo.

^c Includes participants who had a baseline assessment but no post-baseline assessment at the data cutoff date.

^d From Kaplan-Meier method for censored data. Includes three participants with a response of ≥6 mo.

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Data sharing statement: 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 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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2026.03.026>.

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