2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereafter called the Sponsor or MSD)

COMPOUND NAME: pembrolizumab (MK-3475)

PROTOCOL TITLE: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-641)

STUDY IDENTIFIERS:

IND: 122753	EudraCT: 2018-004117-40	WHO: Not applicable	NCT: NCT03834493
JAPIC-CTI: 195005	UTN: Not applicable	EU CT: 2022-500785-10-00	

STUDY PHASE: Phase 3

INDICATION: Prostate cancer

STUDY CENTERS: This study was conducted at 224 centers in 27 countries.

STUDY STATUS:

This study is ongoing; this report is based on the first interim analysis (IA1; data cutoff 12-DEC-2022).

First Participant, First Visit	Data Cutoff	Database Lock Date
28-JUL-2019	IA1 data cutoff of 12-DEC-2022	30-JAN-2023

METHODOLOGY:

This is an ongoing Phase 3, multicenter, efficacy, safety, parallel assignment, double-blind, placebo intervention study of pembrolizumab plus enzalutamide versus placebo plus enzalutamide in participants with mCRPC who are abiraterone-naïve, or who are intolerant to or have progressed on abiraterone acetate.

Enzalutamide refers to enzalutamide plus androgen deprivation therapy (ADT) throughout this document.

After a Screening Phase of up to 42 days, 1244 eligible participants were stratified by prior treatment with abiraterone (yes vs no), metastases (bone only vs liver vs other), and prior docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC) (yes vs no). Participants were then randomly assigned in a 1:1 ratio to receive either pembrolizumab plus enzalutamide (Group 1) or placebo plus enzalutamide (Group 2), as shown in the study interventions table below. Treatment with pembrolizumab was to continue for up to 35 cycles (approximately 2 years), or until blinded independent central review–verified (BICR-verified) radiographic disease progression, or until another protocol-specified discontinuation criterion was met. Participants could have continued enzalutamide until BICR-verified radiographic disease progression or another protocol-specified discontinuation criterion was met.

Participants were evaluated by radiographic imaging at screening, then every 9 weeks from the date of randomization through Week 54, and every 12 weeks thereafter to assess response to treatment during the study. All scheduled images were submitted to a central imaging vendor for independent determination of radiographic progression-free survival (rPFS), objective response rate (ORR), duration of response (DOR), and time to radiographic soft-tissue progression per Prostate Cancer Working Group–modified Response Evaluation Criteria in Solid Tumors Version 1.1 (PCWG-modified RECIST 1.1).

At IA1, data from KEYNOTE-641 were reviewed by an external Data Monitoring Committee (eDMC). After review of IA1 safety and efficacy data, the eDMC recommended stopping the study for futility because it was extremely unlikely that the efficacy boundary for study success would be reached at a future analysis. The eDMC recommendation was based on a lack of efficacy according to the prespecified endpoints but not specific safety issues. Key considerations were as follows:

- At IA1, pembrolizumab plus enzalutamide did not demonstrate a benefit in overall survival (OS) compared to placebo plus enzalutamide and the observed OS hazard ratio (HR) crossed the prespecified OS futility HR boundary.
- At IA1 (the final analysis [FA] for rPFS), pembrolizumab plus enzalutamide did not demonstrate a benefit in rPFS compared to placebo plus enzalutamide.
- The combination of pembrolizumab plus enzalutamide, compared to placebo with enzalutamide, was associated with higher frequencies of Grade 3 to 5 adverse events (AEs), serious adverse events (SAEs), and events leading to discontinuation of the study drug.

Based on these analyses, the Sponsor acknowledged the eDMC's recommendation, unblinded the study, and issued an Important Update and Required Actions letter informing all investigators to notify participants of the study outcome and to evaluate participants in the experimental study arm who may have been deriving clinical benefit. No additional efficacy analyses for OS and rPFS endpoints will be performed. The Sponsor will continue to monitor the safety profile of pembrolizumab and is carefully reviewing the safety data from the KEYNOTE-641 trial. Study participants will be evaluated, discontinued from pembrolizumab or placebo, and be offered standard of care (SOC) treatment options, including continuation on enzalutamide alone, if effective. Study participants who, in the

assessment of their study physician, are benefiting from the combination of enzalutamide and pembrolizumab may continue after consulting with the study medical director. Protocol Amendment-09 was implemented after IA1 to allow participants to continue receiving study intervention or SOC until meeting protocol-specified discontinuation criteria if they were deriving clinical benefit.

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1: Pembro + Enzalutamide	Pembrolizumab	200 mg	Q3W	IV	D1 of each 21-day cycle for up to 35 cycles	Test product
	Enzalutamide	160 mg	QD	PO	Four 40-mg capsules/tablets orally QD or two 80-mg tablets orally QD	SOC
Arm 2: Placebo + Enzalutamide	Placebo	NA	Q3W	IV	D1 of each 21-day cycle for up to 35 cycles	Placebo
	Enzalutamide	160 mg	QD	PO	Four 40-mg capsules/tablets orally QD or two 80-mg tablets orally QD	SOC

D=Day; IV=intravenous; NA=not applicable; PO=by mouth; Q3W=every 3 weeks; QD=once daily; SOC=standard of care.

Part of this study was conducted during the coronavirus disease 2019 (COVID-19) pandemic. The Sponsor continued to follow its standard operating procedures (SOPs) for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

ELIGIBILITY CRITERIA:

Participants who had histologically- or cytologically-confirmed adenocarcinoma of the prostate without small cell histology and prostate cancer progression on ADT (or post bilateral orchiectomy) within 6 months before randomization were enrolled into the study. Participants must also have been either abiraterone-naïve or were to have received and progressed on (or had become intolerant to) abiraterone acetate in the prechemotherapy mHSPC or mCRPC state. Prior docetaxel for mHSPC was allowed if ≥4 weeks had elapsed from the last dose of docetaxel. Prior treatment with a second-generation androgen-receptor inhibitor (eg, enzalutamide) or cytochrome P450 (CYP)17 inhibitor other than abiraterone acetate was prohibited.

OBJECTIVES AND ENDPOINTS:

The following objectives and endpoints were evaluated.

Objectives	Endpoints
Primary	
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **OS** Hypothesis (H1): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to **OS**	**OS:** the time from randomization to death due to any cause
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR where soft-tissue will be assessed per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and bone disease will be assessed per PCWG criteria Hypothesis (H2): The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to **rPFS** per PCWG-modified RECIST 1.1 as assessed by BICR	**rPFS:** the time from randomization to radiographic progression, or death due to any cause, whichever occurs first
Secondary	
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to **the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first (TFST)** Hypothesis 3: The combination of pembrolizumab plus enzalutamide is superior to placebo plus enzalutamide with respect to **TFST**	**TFST:** the time from randomization to initiation of the first subsequent anticancer therapy or death, whichever occurs first

Objectives	Endpoints
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the: **Prostate-specific antigen (PSA) response rate** **PSA undetectable rate** **ORR and DOR per PCWG-modified RECIST 1.1 as assessed by BICR**	**PSA response:** a PSA decline of ≥50% from baseline measured twice at least 3 weeks apart **PSA undetectable:** PSA < 0.2 ng/mL during study intervention **Objective response (OR):** Complete response (CR) or partial response (PR) **DOR:** the time from the earliest date of the first documented evidence of CR or PR until earliest date of disease progression or death due to any cause, whichever occurs first
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the: **Time to PSA progression** **Time to radiographic soft-tissue progression** per soft-tissue rules of PCWG-modified RECIST 1.1, as assessed by BICR **Time to pain progression (TTPP)** based on Brief Pain Inventory-Short Form (BPI-SF) Item 3 "worst pain in 24 hours" and opiate analgesic use (analgesic quantification algorithm [AQA] score) **Time to symptomatic skeletal-related event (SSRE)**	**Time to PSA progression:** the time from randomization to PSA progression. The PSA progression date is defined as the date of 1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, or 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline **Time to radiographic soft-tissue progression:** the time from randomization to radiographic soft-tissue progression **TTPP** based on BPI-SF Item 3 "worst pain in 24 hours" and opiate analgesic use (AQA score) **Time to SSRE:** the time from randomization to the first SSRE, defined as • first use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms • occurrence of new symptomatic pathologic bone fracture (vertebral or nonvertebral) • occurrence of spinal cord compression • or tumor-related orthopedic surgical intervention, whichever occurs first

Objectives	Endpoints
To evaluate the **safety and tolerability** of pembrolizumab plus enzalutamide versus placebo plus enzalutamide	**AEs** Study intervention **discontinuation due to AEs**
Tertiary/Exploratory	
To evaluate efficacy of pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to OS, rPFS, ORR, and DOR in participants with positive programmed cell death ligand 1 (PD-L1) (combined positive score [CPS]>1%) versus all-comers	**OS, rPFS, OR, DOR**
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the **time to radiographic bone progression (TTBP)** per PCWG-modified RECIST 1.1, as assessed by BICR	**TTBP:** the time from randomization to radiographic bone progression
To compare pembrolizumab plus enzalutamide versus placebo plus enzalutamide with respect to the change from baseline disease-related symptoms and health-related quality of life (HRQoL) using **BPI-SF, Functional Assessment of Cancer Therapy-Prostate (FACT-P) and EuroQoL Five-Dimension Five-Level Health State Utility Index (EQ-5D-5L) questionnaires**	**BPI-SF:** progression in pain severity domain, change in pain interference domain, and pain palliation **FACT-P:** FACT-P total score, Functional Assessment of Cancer Therapy-General (FACT-G) total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscale, and FACT Advanced Prostate Symptom Index 6 (FAPSI6) **EQ-5D-5L:** Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression health states and EQ-5D-5L visual analog scale
To characterize health utilities following the administration of pembrolizumab plus enzalutamide versus placebo plus enzalutamide	**EQ-5D-5L**

Objectives	Endpoints
To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab plus enzalutamide versus placebo plus enzalutamide	Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue

The tertiary/exploratory objectives and endpoints results presented in this clinical study report (CSR) are those for analyses by PD-L1 status of OS, rPFS, OR, and DOR, and analyses of TTBP and patient-reported outcome (PRO [BPI-SF, FACT-P, and EQ-5D-5L]). For the EQ-5D-5L, only visual analog scale (VAS) data are presented in this CSR. The 5 health states (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) are not presented. Other tertiary/exploratory objectives and endpoints are also not presented.

NUMBER OF PARTICIPANTS (planned and analyzed): The planned enrollment total was 1240 participants. As of the data cutoff date for this report,1244 participants were randomized (621 in the pembrolizumab plus enzalutamide group, 623 in the placebo plus enzalutamide group). A total of 6 participants in the pembrolizumab plus enzalutamide group and 3 in the placebo plus enzalutamide group did not receive study intervention.

STATISTICAL AND ANALYSIS METHODS:

The prespecified IA1 was performed after observation of approximately 510 OS events and at least approximately 6 months after enrollment completion. This IA1 comprised the FA for the hypotheses of rPFS and TFST and the first interim analysis for the hypothesis of OS. A prespecified non-binding futility analysis for OS was included in IA1 to determine whether there was sufficient evidence to continue the study.

Efficacy analyses were conducted using the Intent-to-Treat (ITT) population, which included all randomized participants. Efficacy data were reported in accordance with the intervention group to which a participant was randomized. Safety analyses were conducted in the All Participants as Treated (APaT) population, which consisted of all randomized participants who received at least 1 dose of study intervention. Safety data were reported in accordance with the actual study intervention received, regardless of intervention group assignment. PRO analyses were based on the PRO Full Analysis Set (FAS) population, defined as participants who had at least 1 PRO assessment available for the specific endpoint and had received at least 1 dose of study intervention. PRO data were reported in accordance with the intervention group to which a participant was randomized.

The nonparametric Kaplan-Meier (KM) method was used to estimate curves of OS, rPFS, and TFST. The treatment differences were assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (ie, HR) between the 2 intervention groups.

The analysis of safety results followed a tiered approach. Analyses in which 95% confidence intervals (CIs) were provided for between-treatment differences in the percentage of participants with events were performed using the Miettinen and Nurminen method.

KEYNOTE-641 did not meet the predefined success criteria for superiority of the dual primary endpoints of OS and rPFS. The observed OS HR crossed the prespecified OS futility HR boundary (HR >1.0), and after review of IA1 safety and efficacy data, the eDMC recommended stopping the study for futility. Since the OS and rPFS hypotheses were not rejected, the TFST hypothesis was not tested. Thus, the *p*-value for TFST presented in this CSR is considered nominal and is not controlled for multiplicity.

RESULTS:

Participant Disposition:

- **Pembrolizumab plus enzalutamide:** 621 randomized, 615 treated, 492 discontinued treatment, 123 ongoing on treatment, 310 discontinued study, 311 ongoing in the study.
- **Placebo plus enzalutamide:** 623 randomized, 620 treated, 485 discontinued treatment, 135 ongoing on treatment, 299 discontinued study, 324 ongoing in the study.

Demographics and Baseline Characteristics:

- **Median Age (Range):** 71.0 years (44 to 93 years)
- **Race:** 20 (1.6%) American Indian or Alaska Native, 166 (13.3%) Asian, 22 (1.8%) black or African American, 25 (2.0%) multiple, 6 (0.5%) Native Hawaiian or other Pacific Islander, 999 (80.3%) white, 6 (0.5%) missing
- **ECOG Status:** 729 (58.6%) score of 0, 507 (40.8%) score of 1, 1 (0.1%) score of 2, 7 (0.6%) missing
- **Prior Treatment with Abiraterone:** 757 (60.9%) with prior abiraterone treatment, 487 (39.1%) without prior abiraterone treatment
- **Prior Treatment with Docetaxel for Metastatic Hormone-Sensitive Prostate Cancer:** 362 (29.1%) with prior docetaxel treatment, 882 (70.9%) without prior docetaxel treatment
- **Metastases at Baseline:** 616 (49.5%) with bone only, 54 (4.3%) with liver, 574 (46.1%) with other

Efficacy:

At IA1, KEYNOTE-641 did not meet the predefined success criteria for superiority of the dual primary endpoints of OS and rPFS. In addition, the observed OS HR crossed the prespecified OS futility HR boundary (HR >1.0). There was generally no favorable trend in primary and secondary endpoints for participants receiving pembrolizumab plus enzalutamide versus placebo plus enzalutamide.

Primary Efficacy Endpoints

- The OS HR was 1.04 (95% CI: 0.88, 1.22); *p*=0.6621, with a median OS of 24.7 months in the pembrolizumab plus enzalutamide group and 27.3 months in the placebo plus enzalutamide group.
- The rPFS HR (based on BICR) was 0.98 (95% CI: 0.84, 1.14); *p*=0.4073, with a median rPFS of 10.4 months in the pembrolizumab plus enzalutamide group and 9.0 months in the placebo plus enzalutamide group.

Key Secondary Efficacy Endpoints

- The TFST HR was 0.95 (95% CI: 0.83, 1.09), with a median TFST of 13.2 months in the pembrolizumab plus enzalutamide group and 12.6 months in the placebo plus enzalutamide group.

Other Secondary Efficacy Endpoints

- CCI [redacted]
- CCI [redacted]
- ORR based on BICR in participants with measurable disease at baseline was 32.2% in the pembrolizumab plus enzalutamide group.
- CCI [redacted]
- CCI [redacted]

- CCI
- CCI
- CCI

Safety:

Pembrolizumab in combination with enzalutamide demonstrated a manageable safety profile in participants with mCRPC.

- The frequencies of most AE categories were higher in the pembrolizumab plus enzalutamide group compared with the placebo plus enzalutamide group.
- Following exposure adjustment, the safety profile in the pembrolizumab plus enzalutamide group was generally consistent with the safety profile anticipated for the component drugs when administered as monotherapy.
- No new adverse events of special interest (AEOSI) were identified for this study. The frequency of AEOSI in the pembrolizumab plus enzalutamide group was higher than in the established safety profile of pembrolizumab monotherapy. This was driven by an increased incidence of Severe Skin Reactions, which was likely due to the immunomodulatory effects of enzalutamide. Outcomes, reversibility, and AE management for Severe Skin Reactions in the pembrolizumab plus enzalutamide group were generally consistent with those for Severe Skin Reactions associated with the established safety profile of pembrolizumab monotherapy. Skin adverse drug reactions (ADRs) are known for both pembrolizumab and enzalutamide as monotherapies.
- The incidence of fatal AEs in the pembrolizumab plus enzalutamide group was higher compared with the placebo plus enzalutamide group (5.9% in the pembrolizumab plus enzalutamide group versus 2.4% in the placebo plus enzalutamide group). The incidence of fatal AEs in the pembrolizumab plus enzalutamide group was consistent with the established safety profile of pembrolizumab monotherapy. Incidences of individual fatal AEs in the pembrolizumab plus enzalutamide group did not exceed 1%, and most fatal AEs were reported in single participants. No new safety concerns were identified.
- The AEs observed for the combination intervention group were effectively managed by standard clinical practice as applicable to pembrolizumab or enzalutamide monotherapy.

Adverse Event Summary
(APaT Population)

	Pembrolizumab + Enzalutamide		Placebo + Enzalutamide	
	n	(%)	n	(%)
Participants in population	615		620	
with one or more adverse events	594	(96.6)	596	(96.1)
with no adverse event	21	(3.4)	24	(3.9)
with drug-related[a] adverse events	479	(77.9)	382	(61.6)
with toxicity grade 3-5 adverse events	343	(55.8)	254	(41.0)
with toxicity grade 3-5 drug-related adverse events	192	(31.2)	67	(10.8)
with serious adverse events	237	(38.5)	165	(26.6)
with serious drug-related adverse events	89	(14.5)	20	(3.2)
who died	36	(5.9)	15	(2.4)
who died due to a drug-related adverse event	3	(0.5)	0	(0.0)
discontinued any drug due to an adverse event	115	(18.7)	50	(8.1)
discontinued Pembrolizumab/Placebo	109	(17.7)	39	(6.3)
discontinued Enzalutamide	69	(11.2)	37	(6.0)
discontinued Pembrolizumab/Placebo and Enzalutamide	55	(8.9)	25	(4.0)
discontinued any drug due to a drug-related adverse event	71	(11.5)	21	(3.4)
discontinued Pembrolizumab/Placebo	71	(11.5)	13	(2.1)
discontinued Enzalutamide	23	(3.7)	14	(2.3)
discontinued Pembrolizumab/Placebo and Enzalutamide	19	(3.1)	6	(1.0)
discontinued any drug due to a serious adverse event	84	(13.7)	32	(5.2)
discontinued Pembrolizumab/Placebo	78	(12.7)	27	(4.4)
discontinued Enzalutamide	56	(9.1)	26	(4.2)
discontinued Pembrolizumab/Placebo and Enzalutamide	48	(7.8)	21	(3.4)
discontinued any drug due to a serious drug-related adverse event	44	(7.2)	8	(1.3)
discontinued Pembrolizumab/Placebo	43	(7.0)	5	(0.8)
discontinued Enzalutamide	15	(2.4)	6	(1.0)

Adverse Event Summary
(APaT Population)

	Pembrolizumab + Enzalutamide		Placebo + Enzalutamide	
	n	(%)	n	(%)
discontinued Pembrolizumab/Placebo and Enzalutamide	14	(2.3)	3	(0.5)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.03.

Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.

MedDRA V25.1 preferred terms 'Neoplasm progression', 'Malignant neoplasm progression' and 'Disease progression' not related to the drug are excluded.

Database Cutoff Date: 12DEC2022.

Source: [P641V01MK3475: adam-adsl; adae]

CONCLUSIONS:

Efficacy

KEYNOTE-641 did not meet the predefined success criteria for superiority of the dual primary endpoints of OS and rPFS. The observed OS HR crossed the prespecified OS futility HR boundary.

Safety

Pembrolizumab in combination with enzalutamide demonstrated a manageable safety profile in participants with mCRPC that was generally consistent with the safety profile anticipated for the component drugs when administered as monotherapy.

PUBLICATIONS:

Graff JN, Burgents J, Liang LW, Stenzl A. KEYNOTE 641: Phase 3 Study of Pembrolizumab (pembro) Plus Enzalutamide for Metastatic Castration-Resistant Prostate Cancer (mCRPC). *Ann Oncol*. 2019;30(suppl 5):v325-v355. doi:10.1093/annonc/mdz248

Graff JN, Burgents J, Liang LW, Stenzl A. Phase III study of pembrolizumab (pembro) plus enzalutamide (enza) versus placebo plus enza for metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE 641. *J Clin Oncol*. 2020;38(suppl 6):TPS258. doi:10.1200/JCO.2020.38.6_suppl.TPS258

Graff JN, Liang LW, Kim J, Stenzl A. KEYNOTE-641: a Phase III study of pembrolizumab plus enzalutamide for metastatic castration-resistant prostate cancer. *Future Oncol*. 2021;17(23):3017-3026. doi:10.2217/fon-2020-1008

REPORT DATE: 06-JUL-2023

REVISED REPORT DATE: Not applicable