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 Plus ADT Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (KEYNOTE-991)

STUDY IDENTIFIERS:

IND: 122753	EudraCT: 2019-003633-41	WHO: Not applicable	NCT: NCT04191096
JAPIC-CTI: Not applicable	UTN: Not applicable	EU CT: Not applicable	

STUDY PHASE: Phase 3

INDICATION: Prostate cancer

STUDY CENTERS: This study was conducted at 213 centers in 29 countries.

STUDY STATUS:

This study is ongoing; this report is based on the first interim analysis (IA1; data cutoff of 31-OCT-2022).

First Participant, First Visit	**Data Cutoff**	**Database Lock Date**
12-FEB-2020	IA1 data cutoff of 31-OCT-2022	14-DEC-2022

METHODOLOGY:

KEYNOTE-991 is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of pembrolizumab plus enzalutamide plus androgen deprivation therapy (ADT) versus placebo plus enzalutamide plus ADT in participants with metastatic hormone-sensitive prostate cancer (mHSPC).

The study enrolled 2 portions: global and China extension enrollment. Participants enrolled during the global enrollment period are the focus of this clinical study report (CSR).

After a screening phase of up to 42 days in the global portion, 1251 participants were stratified according to the following factors:

- Prior docetaxel for mHSPC: Yes versus No
- High-volume disease: Yes versus No

and randomly assigned in a 1:1 ratio to 1 of the following 2 intervention groups:

- Group 1: pembrolizumab plus enzalutamide plus ADT
  (referred to as the "pembrolizumab plus enzalutamide group" in this CSR)
- Group 2: placebo plus enzalutamide plus ADT
  (referred to as the "placebo plus enzalutamide group" in this CSR)

Treatment with pembrolizumab/placebo was to continue for 35 cycles (approximately 2 years starting with the first infusion in Cycle 1) or until blinded independent central review–verified (BICR-verified) disease progression, unacceptable adverse events (AEs), or meeting other protocol-specified criteria for discontinuation. Enzalutamide treatment was to begin on the same day as Day 1 Cycle 1 of pembrolizumab/placebo and was to follow a daily dosing cycle until criteria for discontinuation were met. Participants who discontinued 1 of the 2 treatments due to drug-related AEs could continue with the other combination partner until criteria for discontinuation were met.

Eligible participants who completed 35 cycles or were discontinued due to complete response (CR) were offered a second course with an additional 17 cycles (approximately 1 year) of pembrolizumab after BICR-verified progressive disease.

On-study imaging assessments were performed every 12 weeks (84 days ± 7 days) from the date of randomization and submitted to a central imaging vendor for independent review.

At IA1, data from KEYNOTE-991 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:

- Pembrolizumab plus enzalutamide plus ADT did not demonstrate a benefit in radiographic progression-free survival (rPFS), the study's first dual primary endpoint, compared to placebo plus enzalutamide plus ADT, and is unlikely to do so at future analyses. The study's other dual primary endpoint, overall survival (OS), did not demonstrate improvement compared to the control arm and appears unlikely to do so at a future analysis.

- Pembrolizumab plus enzalutamide plus ADT, compared to placebo plus enzalutamide plus ADT, was associated with higher frequencies of Grade 3 to 5 AEs, serious AEs (SAEs), AEs leading to death, and AEs leading to discontinuation of study intervention.

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 rPFS and OS 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-991 trial. Study participants will be evaluated, discontinued from pembrolizumab or placebo, and offered standard of care treatment options, including continuation on enzalutamide plus ADT 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-04 was implemented after IA1 to allow participants to continue receiving study intervention or standard of care 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	Test Product
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	Test Product

Abbreviations: D=Day; IV=intravenous; NA=not applicable; PO=oral; Q3W=every 3 weeks; QD=once daily

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its standard operating procedures 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:

Male participants ≥18 years of age with mHSPC (histologically or cytologically-confirmed prostate adenocarcinoma without small cell histology), with BICR-verified metastatic disease beyond the lymph nodes (≥2 bone lesions and/or visceral disease), and naïve to next-generation hormonal agents were enrolled in this study.

OBJECTIVES AND ENDPOINTS:

In participants with mHSPC:

Objectives	Endpoints
Primary	
• To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **rPFS** per Prostate Cancer Working Group–modified (PCWG-modified) Response Evaluation Criteria in Solid Tumors Version 1.1 (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 (H1): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT 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.

Objectives	Endpoints
• To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **OS**. • Hypothesis (H2): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **OS**.	• **OS:** the time from randomization to death due to any cause.
Secondary	
• To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **time to initiation of the first subsequent anticancer therapy (TFST)**. • Hypothesis (H3): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **TFST**.	• **TFST:** the time from randomization to initiation of the first subsequent anti-cancer therapy or death, whichever comes first.
• To compare pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to **time to symptomatic skeletal-related event (TTSSRE)**. • Hypothesis (H4): The combination of pembrolizumab plus enzalutamide plus ADT is superior to placebo plus enzalutamide plus ADT with respect to **TTSSRE.**	**TTSSRE:** the time from randomization to the first SSRE, defined as • use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms • occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral) • occurrence of spinal cord compression • or tumor-related orthopedic surgical intervention, whichever occurs first

Objectives	Endpoints
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the: • **Time to prostate-specific antigen (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)** • **Time from randomization to disease progression (PFS2)** as determined by investigator assessment	• **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:** time from randomization to pain progression based on Brief Pain Inventory-Short Form (BPI-SF) Item 3 "worst pain in 24 hours" and opioid use • **PFS2:** Time from randomization to disease progression as determined by investigator assessment of radiological or clinical progression after next-line of therapy or death from any cause, whichever occurs first
To assess pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT with respect to the: • **PSA response rate** • **PSA undetectable rate** • **Objective response rate (ORR) and duration of response (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):** 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

Objectives	Endpoints
• To assess the **safety and tolerability** of pembrolizumab plus enzalutamide plus ADT versus placebo plus enzalutamide plus ADT	• **AEs** • Study intervention **discontinuation due to AEs**
Tertiary/Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

CCI [redacted]

NUMBER OF PARTICIPANTS (planned and analyzed):

The planned enrollment total was 1232 participants in the global study. In the extension portion in China, approximately 186 participants were planned to be enrolled. This report only addresses the global portion of the study.

As of the data cutoff date for this report, 1251 participants were randomized in the global portion (626 in the pembrolizumab plus enzalutamide group, and 625 in the placebo plus enzalutamide group). One randomized participant in the pembrolizumab plus enzalutamide group did not receive study intervention.

STATISTICAL AND ANALYSIS METHODS:

CCI [redacted] IAs and 1 final analysis were planned for this study. IA1 was to be performed approximately CCI [redacted] months after the first participant was randomized, and the primary purpose of IA1 was to provide an interim analysis for CCI [redacted]

The intent to treat (ITT) population, defined as all randomized participants, served as the primary population for the analysis of efficacy data in this study (1251 participants). The participants in China who were randomized in the extension portion were not included in the primary efficacy analysis population for the global portion. The China ITT population, including all participants in China randomized in the global portion and the extension portion, will be analyzed later.

The hypotheses were evaluated by comparing the pembrolizumab plus enzalutamide group to the placebo plus enzalutamide group with respect to rPFS, OS, TFST, and TTSSRE using a stratified log-rank test. The hazard ratio was estimated using a stratified Cox regression model with Efron's method of tie handling. Event rates over time were estimated within each treatment group using the Kaplan-Meier method.

KEYNOTE-991 did not meet the predefined success criteria for superiority of the dual primary endpoints of rPFS and OS. After review of IA1 safety and efficacy data, the eDMC recommended stopping the study for futility. No further hypothesis testing was conducted. Per the multiplicity strategy in the protocol, all initial alpha was allocated to rPFS. Since the rPFS hypothesis was not rejected, CCI [redacted] were not tested. Except for the *p*-value of rPFS, *p*-values for all endpoints are considered nominal and are not controlled for multiplicity.

The safety analyses were conducted using the all participants as treated (APaT) population, which included all randomized participants who received at least 1 dose of study intervention (1250 participants).

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

RESULTS:

Participant Disposition:

- **Pembrolizumab plus enzalutamide group:** 626 randomized, 625 treated, 221 discontinued treatment, 404 ongoing on treatment, 108 discontinued study, and 518 ongoing in the study

- **Placebo plus enzalutamide group:** 625 randomized, 625 treated, 201 discontinued treatment, 424 ongoing on treatment, 95 discontinued study, and 530 ongoing in the study

Demographics and Baseline Characteristics:

- **Overall Median Age (Range)**: 68.0 years (range: 37 to 91)

- **Ethnicity:** 1015 (81.1%) not Hispanic or Latino, 231 (18.5%) Hispanic or Latino, 2 (0.2%) not reported, and 3 (0.2%) unknown

- **Race:** 32 (2.6%) American Indian or Alaska Native, 217 (17.3%) Asian, 31 (2.5%) black or African American, 76 (6.1%) multiple, 4 (0.3%) Native Hawaiian or Other Pacific Islander, 887 (70.9%) white, and 4 (0.3%) missing

Efficacy:

At IA1, KEYNOTE-991 did not meet the predefined success criteria for superiority of the dual primary endpoints of rPFS and OS. 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 rPFS HR (based on BICR) was 1.20 (95% CI: 0.96, 1.49); *p*=0.9467. The median rPFS was not reached in either intervention group.

- At IA1, OS was not tested since all initial alpha was allocated to rPFS, and the rPFS hypothesis was not rejected. The OS HR was 1.16 (95% CI: 0.88, 1.53). The median OS was not reached in either intervention group.

Key Secondary Efficacy Endpoints

- The TFST HR was 1.24 (95% CI: 1.01, 1.54) and the median TFST was not reached in either intervention group.

- The TTSSRE HR of 0.89 (95% CI: 0.61, 1.30) and the median TTSSRE was not reached in either intervention group.

Other Secondary Efficacy Endpoints

The following are key results for the secondary endpoints:

- The PSA response rate in participants with PSA measurement(s) at baseline was 90.3% in the pembrolizumab plus enzalutamide group and 93.0% in the placebo plus enzalutamide group.

- The PSA undetectable rate in participants with detectable PSA at baseline was 63.4% in the pembrolizumab plus enzalutamide group and 64.1% in the placebo plus enzalutamide group.

- ORR based on BICR in participants with measurable disease at baseline was 65.7% in the pembrolizumab plus enzalutamide group and 71.8% in the placebo plus enzalutamide group.

- The median time to response (TTR) based on BICR in confirmed responders of participants with measurable disease at baseline was 2.9 months in both intervention groups. The median DOR based on BICR in confirmed responders of participants with measurable disease at baseline was not reached in either intervention group.

- The time to PSA progression HR was 0.92 (95% CI: 0.69, 1.23) and the median time to PSA progression was not reached in either intervention group.

- The time to radiographic soft tissue progression HR was 1.07 (95% CI: 0.81, 1.41) based on BICR. The median time to radiographic soft tissue progression was not reached in either intervention group.

- The time to PFS2 HR was 1.16 (95% CI: 0.90, 1.50) based on investigator assessment The median time to PFS2 was not reached in either intervention group.

- The TTPP HR was 1.15 (95% CI: 0.95, 1.39) and the median number of event-free months was not reached either intervention group.

Safety:

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

- 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 a monotherapy.

- The frequency of adverse events of special interest (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 (5.3% in the pembrolizumab plus enzalutamide group versus 2.6% 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 + ADT		Placebo + Enzalutamide + ADT	
	n	(%)	n	(%)
Participants in population	625		625	
with one or more adverse events	618	(98.9)	595	(95.2)
with no adverse event	7	(1.1)	30	(4.8)
with drug-related[a] adverse events	550	(88.0)	419	(67.0)
with toxicity grade 3-5 adverse events	387	(61.9)	238	(38.1)
with toxicity grade 3-5 drug-related adverse events	261	(41.8)	87	(13.9)
with serious adverse events	252	(40.3)	145	(23.2)
with serious drug-related adverse events	114	(18.2)	18	(2.9)
who died	33	(5.3)	16	(2.6)
who died due to a drug-related adverse event	6	(1.0)	1	(0.2)
discontinued any drug due to an adverse event	209	(33.4)	51	(8.2)
discontinued Pembrolizumab/Placebo	203	(32.5)	43	(6.9)
discontinued Enzalutamide	82	(13.1)	36	(5.8)
discontinued Pembrolizumab/Placebo and Enzalutamide	68	(10.9)	25	(4.0)
discontinued any drug due to a drug-related adverse event	171	(27.4)	27	(4.3)
discontinued Pembrolizumab/Placebo	167	(26.7)	19	(3.0)
discontinued Enzalutamide	47	(7.5)	14	(2.2)
discontinued Pembrolizumab/Placebo and Enzalutamide	37	(5.9)	6	(1.0)
discontinued any drug due to a serious adverse event	115	(18.4)	30	(4.8)

Adverse Event Summary
(APaT Population)

	Pembrolizumab + Enzalutamide + ADT		Placebo + Enzalutamide + ADT	
	n	(%)	n	(%)
discontinued Pembrolizumab/Placebo	111	(17.8)	28	(4.5)
discontinued Enzalutamide	61	(9.8)	22	(3.5)
discontinued Pembrolizumab/Placebo and Enzalutamide	54	(8.6)	18	(2.9)
discontinued any drug due to a serious drug-related adverse event	80	(12.8)	9	(1.4)
discontinued Pembrolizumab/Placebo	79	(12.6)	8	(1.3)
discontinued Enzalutamide	28	(4.5)	3	(0.5)
discontinued Pembrolizumab/Placebo and Enzalutamide	25	(4.0)	2	(0.3)

[a] Determined by the investigator to be related to the drug.
Grades are based on NCI CTCAE version 5.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of 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: 31OCT2022.

Source: [P991V01MK3475: adam-adsl; adae]

CONCLUSIONS:

Efficacy

KEYNOTE-991 did not meet the predefined success criteria for superiority of the dual primary endpoints of rPFS and OS.

Safety

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

PUBLICATIONS:

Gratzke C, Niu C, Poehlein CH, Burgents JE. KEYNOTE-991: Phase 3 Study of Pembrolizumab (pembro) Plus Enzalutamide (enza) and Androgen Deprivation Therapy (ADT) for Patients (pts) With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC). Deutsche Gesellschaft fur Urologie 73rd Congress. DGU. 2021.

Gratzke C, Niu C, Poehlein CH, Burgents JE. Pembrolizumab (pembro) Plus Enzalutamide (enza) and Androgen Deprivation Therapy (ADT) for Patients (pts) With Metastatic Hormone-sensitive Prostate Cancer (mHSPC): the Phase 3 KEYNOTE-991 Study. J Clin Oncol (ASCO-GU). ASCO-GU. 2021;39(Suppl 6): TPS184. doi:10.1200/JCO.2021.39.6_suppl.TPS184 ascopubs.org/doi/10.1200/JCO.2021.39.6_suppl.TPS184.

Gratzke C, Niu C, Poehlein CH, Burgents JE. KEYNOTE-991: Phase 3 Study of Pembrolizumab Plus Enzalutamide and Androgen Deprivation Therapy (ADT) for Patients With Metastatic Hormone-sensitive Prostate Cancer (mHSPC). Society for Immunotherapy of Cancer - 35th Annual Meeting. SITC. 2020;8(3): A371. doi:10.1136/jitc-2020-SITC2020.0346 https://jitc.bmj.com/ content/8/Suppl_3/A371.

Gratzke C, Burgents JE, Niu C, Poehlein CH, Drake CG. Phase 3 Study of Pembrolizumab (pembro) Plus Enzalutamide (enza) and Androgen Deprivation Therapy (ADT) for Patients (pts) With Metastatic Hormone-sensitive Prostate Cancer (mHSPC): KEYNOTE-991. J Clin Oncol (ASCO). ASCO. 2020;38(Suppl 15): TPS5595. doi:10.1200/JCO.2020.38.15_suppl.TPS5595+ https://meetinglibrary.asco.org/record/191766/abstract.

REPORT DATE: 16-JUN-2023

REVISED REPORT DATE: Not applicable