2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: Pembrolizumab (MK-3475)

PROTOCOL TITLE: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564)

STUDY IDENTIFIERS:

IND: 122753	EudraCT: 2016-004351-75	WHO: N/A	NCT: NCT03142334
Other: N/A			

STUDY PHASE: 3

INDICATION: Adjuvant treatment of patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

STUDY CENTERS: This study was conducted at 212 centers in 21 countries.

STUDY STATUS: This study is ongoing; this report is based on the first planned interim analysis (IA1).

First Patient, First Visit	Last Patient, Last Visit	Database Lock Date
30-JUN-2017	14-DEC-2020	26-JAN-2021

NOTE: Patient = Participant

METHODOLOGY: This is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study to evaluate the efficacy and safety of pembrolizumab in the adjuvant treatment of RCC following nephrectomy. Participants have RCC with clear cell component with intermediate-high or high risk of recurrence following nephrectomy or M1 NED following nephrectomy and resection of metastatic lesions. Risk categories were based on pathological tumor-node-metastasis staging, Fuhrman grade, and presence of sarcomatoid features. The intermediate-high risk category included pT2 with Grade 4 or sarcomatoid features; pT3, any grade without nodal involvement (N0) or distant metastases (M0). The high risk category included pT4, any grade N0 and M0, any pT, any grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. The patient population will be referred to herein as patients with RCC at intermediate-high or high risk of recurrence. A total of 994 eligible participants were randomized 1:1 to receive pembrolizumab 200 mg or placebo every 3 weeks for up to 17 cycles (approximately 1 year) or until confirmation of disease recurrence or meeting the criteria for discontinuation of study

treatment as outlined in the study protocol. Randomization was stratified by metastasis status (M0 vs M1 NED). Within the M0 group, there were 2 stratification factors: 1) Eastern Cooperative Oncology Group Performance Status (ECOG PS 0 versus 1) and 2) United States (US) participant (yes versus no). After randomization, participants were evaluated with radiographic imaging to assess disease status and response to treatment. All participants who completed 17 cycles or discontinue from treatment for a reason other than disease recurrence were to undergo radiographic imaging follow-up (every 12 weeks during year 1, every 16 weeks during years 2 to 4, then every 24 weeks in years 5 and beyond) for assessment of disease-free survival (DFS).

Part of this study was conducted during the 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.

Treatment	Regimen	Route of Administration	Duration of Treatment
Pembrolizumab	200 mg every 3 weeks	Intravenous infusion	17 cycles (approximately 12 months)
Placebo (saline solution)	0 mg every 3 weeks	Intravenous infusion	17 cycles (approximately 12 months)

ELIGIBILITY CRITERIA: The study included participants with histologically confirmed RCC with clear cell component with intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions (see definitions above); no prior systemic therapy for advanced RCC; ECOG PS of 0 or 1; had undergone a partial nephroprotective or radical complete nephrectomy with compete resection of solid, isolated soft tissue metastatic lesions (M1 NED participants); and were assessed by the investigator as tumor free based on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest, abdomen, and pelvis and a bone scan.

OBJECTIVES AND ENDPOINTS:

Primary Objective(s)	Primary Endpoint(s)
To compare DFS as assessed by the investigator for participants treated with pembrolizumab vs those receiving placebo	DFS as assessed by the investigator, time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first
Secondary Objective(s)	**Secondary Endpoint(s)**
Key Secondary	
To compare OS for participants treated with pembrolizumab vs those receiving placebo	OS, time from randomization to death due to any cause

Other Secondary	
To compare the safety and tolerability profiles for participants treated with pembrolizumab vs those receiving placebo	Adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, deaths, laboratory values, and vital signs
To compare measures of disease recurrence-specific survival (DRSS) as assessed by the investigator, in participants treated with pembrolizumab vs those receiving placebo	DRSS1 as assessed by the investigator, time from randomization to the first documented local recurrence of RCC DRSS2 as assessed by the investigator, time from randomization to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first
To compare event-free survival (EFS) as assessed by the blinded independent radiology review for participants treated with pembrolizumab vs those receiving placebo	EFS as assessed by blinded independent central review (BICR), time from randomization to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants, who by BICR were considered M0/M1 NED; or disease progression among participants, who by BICR were considered to have M1, or death due to any cause, whichever occurs first
To compare DFS and OS according to participants' programmed cell death-ligand 1 (PD-L1) expression status (positive, negative) for participants treated with pembrolizumab vs those receiving placebo	DFS as assessed by the investigator, time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first OS, time from randomization to death due to any cause
To evaluate patient-reported outcomes (PROs) with European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy Kidney Symptom Index Disease Related Symptoms (FKSI-DRS)	Mean change from baseline in EORTC QLQ-C30 global health status/quality of life scores Mean change from baseline in EORTC QLQ-C30 functional subscales: physical functioning Mean change from baseline in FKSI-DRS score

NUMBER OF PARTICIPANTS (planned and analyzed): Approximately 950 participants were planned to be enrolled/randomized. As of the data cutoff date for this report of IA1, 994 participants were randomized (496 in the pembrolizumab group, 498 in the placebo group).

STATISTICAL METHODS: IA1 was planned to be conducted when approximately 80% of the final 332 required disease recurrence events (approximately 265 DFS events) had accrued plus a minimum 12 months of follow-up from the last participant randomized. Approximately 47% of the final required 200 OS events (approximately 94 OS events) were expected at that time. As of the data cutoff date of IA1 (14-DEC-2020), 260 DFS events had occurred (78% of the total planned events at the final analysis) with a minimum follow-up of 15 months from the last participant randomized, and 51 OS events had occurred (26% of the total planned events at the final analysis).

For IA1, efficacy analyses were conducted using the intention-to-treat (ITT) population, and 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. DFS and OS were evaluated by comparing pembrolizumab to placebo using a stratified log-rank test. Estimation of the hazard ratio (HR) was performed using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier (KM) method. The Maurer and Bretz multiplicity strategy for group-sequential design was applied for the primary endpoint of DFS and key secondary endpoint of OS to provide strong control of the type I error.

The analysis of safety results follows a tiered approach. The tiers differ with respect to the analyses performed. There were no Tier 1 events in this study. Tier 2 parameters were assessed via point estimates with 95% confidence intervals (CIs) provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 safety parameters. The 95% CI for the between-treatment differences in percentages were provided using the Miettinen and Nurminen method.

RESULTS:

Disposition, Demographics and Baseline Characteristics:

Number of participants randomized/allocated/treated/ongoing/discontinued:

- Pembrolizumab: 496 participants were randomized, 488 (98.4%) were treated; of the 488 treated participants, 298 (61.1%) completed study intervention, and 190 (38.9%) discontinued study intervention. Study intervention is ongoing for 0 participants in the pembrolizumab treatment group.

- Placebo: 498 participants were randomized, 496 (99.6%) were treated, 365 (73.6%) completed study intervention, and 130 (26.2%) discontinued study intervention. Study intervention was reported as ongoing for 1 participant. The participant for whom study intervention was reported as ongoing at the time of the data cutoff date for IA1 had received the last dose of study treatment (Cycle 17) but had not completed the study treatment discontinuation visit at the time of the data cutoff date. There were no participants in either treatment group who remained on study treatment at the time of this report.

Overall Median Age (range): 60.0 years (25 to 84 years); Pembrolizumab: 60.0 years (27 to 81 years); Placebo: 60.0 years (25 to 84 years)

Sex: Pembrolizumab: 347 (70.0%) male, 149 (30.0%) female; Placebo: 359 (72.1%) male, 139 (27.9%) female

Ethnicity: Pembrolizumab: 381 (76.8%) not Hispanic or Latino, 72 (14.5%) Hispanic or Latino, 21 (4.2%) not reported, 21 (4.2%) unknown, 1 (0.2%) missing; Placebo: 394 (79.1%) not Hispanic or Latino, 62 (12.4%) Hispanic or Latino, 20 (4.0%) not reported, 21 (4.2%) unknown, 1 (0.2%) missing.

Race: Pembrolizumab: 372 (75%) white, 63 (12.7%) Asian, 36 (7.3%) missing, 8 (1.6%) multiple, 7 (1.4%) black or African American; Placebo: 377 (75.7%) white, 75 (15.1%) Asian, 34 (6.8%) missing, 5 (1.0%) multiple, 5 (1.0%) black or African American.

Efficacy:

- At the prespecified 2.5% overall alpha level (one-sided), pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS compared with placebo (median DFS was not reached in either group; HR: 0.68 [95% CI: 0.53, 0.87]; and p-value 0.0010, p-value boundary: 0.0114).
- Consistent benefit in DFS was observed across prespecified subgroups.
- The OS data were immature at IA1 with 51 deaths (26% of total planned OS events at the final analysis). For OS, the HR was 0.54 (95% CI: 0.30, 0.96) (p=0.0164037) and the median OS was not reached in either group. The p-value did not cross the statistical hypothesis testing p-value boundary of 9.3×10^{-6} at IA1. The upper bound of the 95% CI for the OS HR was below 1.0, with nearly twice as many deaths in the placebo group (33) compared with the pembrolizumab group (18).
- Investigator review and BICR of disease recurrence were generally concordant, and there was no evidence of systematic bias in disease recurrence assessments by investigator favoring the pembrolizumab group based on estimation of differential discordance of disease recurrence based on investigator review versus BICR.
- EFS by BICR showed consistent findings with the primary endpoint of DFS per investigator's assessment.

- PRO assessments, including FKSI-DRS scale, EORTC QLQ-C30 global health status/QoL scale, EORTC QLQ-C30 functional scales, and EORTC QLQ-C30 symptom scales, generally showed that no clinically meaningful mean change from baseline scores was observed within the pembrolizumab and placebo groups at Week 52, and the 95% CIs generally overlapped, which suggests no meaningful difference between treatment groups. These findings suggest that health-related QoL and symptoms scores were stable in the pembrolizumab group over time.

Safety: Adverse events summary data for IA1 (14-DEC-2020 data cutoff) are shown in the following table.

Adverse Event Summary
AEOSI Overall
(APaT Population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	173	(35.5)	34	(6.9)
with no adverse event	315	(64.5)	462	(93.1)
with drug-related[a] adverse events	155	(31.8)	22	(4.4)
with toxicity grade 3-5 adverse events	44	(9.0)	3	(0.6)
with toxicity grade 3-5 drug-related adverse events	43	(8.8)	0	(0.0)
with serious adverse events	41	(8.4)	1	(0.2)
with serious drug-related adverse events	39	(8.0)	1	(0.2)
who died	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	39	(8.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	38	(7.8)	0	(0.0)
discontinued drug due to a serious adverse event	21	(4.3)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	21	(4.3)	0	(0.0)

[a] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.
Database Cutoff Date: 14DEC2020.

Source: [P564V01MK3475: adam-adsl; adae]

CONCLUSIONS:

Efficacy:

- Participants enrolled in this study are representative of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. In this study, adjuvant therapy with pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS, compared with placebo, in this patient population.

Safety:

Pembrolizumab administered in the study population is well tolerated and has an acceptable safety profile.

- The safety and tolerability of pembrolizumab administered in the adjuvant setting is generally consistent with the established safety profile of pembrolizumab monotherapy.
- No new safety signals or new immune-mediated AEs were observed with the use of pembrolizumab in the adjuvant setting.

PUBLICATION(S): As of the date of this report, there are no publications based on this study.

REPORT DATE: 27-MAY-2021

REVISED REPORT DATE: 07-JUN-2021