Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background The first interim analysis of the KEYNOTE-564 study showed improved disease-free survival with adjuvant pembrolizumab compared with placebo after surgery in patients with clear cell renal cell carcinoma at an increased risk of recurrence. The analysis reported here, with an additional 6 months of follow-up, was designed to assess longer-term efficacy and safety of pembrolizumab versus placebo, as well as additional secondary and exploratory endpoints.

Methods In the multicentre, randomised, double-blind, placebo-controlled, phase 3 KEYNOTE-564 trial, adults aged 18 years or older with clear cell renal cell carcinoma with an increased risk of recurrence were enrolled at 213 hospitals and cancer centres in North America, South America, Europe, Asia, and Australia. Eligible participants had an Eastern Cooperative Oncology Group performance status of 0 or 1, had undergone nephrectomy 12 weeks or less before randomisation, and had not received previous systemic therapy for advanced renal cell carcinoma. Participants were randomly assigned (1:1) via central permuted block randomisation (block size of four) to receive pembrolizumab 200 mg or placebo intravenously every 3 weeks for up to 17 cycles. Randomisation was stratified by metastatic disease status (M0 *vs* M1), and the M0 group was further stratified by ECOG performance status and geographical region. All participants and investigators involved in study treatment administration were masked to the treatment group assignment. The primary endpoint was disease-free survival by investigator assessment in the intention-to-treat population (all participants randomly assigned to a treatment). Safety was assessed in the safety population, comprising all participants who received at least one dose of pembrolizumab or placebo. As the primary endpoint was met at the first interim analysis, updated data are reported without p values. This study is ongoing, but no longer recruiting, and is registered with ClinicalTrials.gov, NCT03142334.

Findings Between June 30, 2017, and Sept 20, 2019, 994 participants were assigned to receive pembrolizumab (n=496) or placebo (n=498). Median follow-up, defined as the time from randomisation to data cutoff (June 14, 2021), was 30·1 months (IQR 25·7–36·7). Disease-free survival was better with pembrolizumab compared with placebo (HR 0·63 [95% CI 0·50–0·80]). Median disease-free survival was not reached in either group. The most common all-cause grade 3–4 adverse events were hypertension (in 14 [3%] of 496 participants) and increased alanine aminotransferase (in 11 [2%]) in the pembrolizumab group, and hypertension (in 13 [3%] of 498 participants) in the placebo group. Serious adverse events attributed to study treatment occurred in 59 (12%) participants in the pembrolizumab group and one (<1%) participant in the placebo group. No deaths were attributed to pembrolizumab.

Interpretation Updated results from KEYNOTE-564 support the use of adjuvant pembrolizumab monotherapy as a standard of care for participants with renal cell carcinoma with an increased risk of recurrence after nephrectomy.

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Introduction

Post-nephrectomy adjuvant treatment for renal cell carcinoma has shown no consistent benefit despite 30 years of clinical investigation. VEGF tyrosine-kinase inhibitors have been heavily studied in the adjuvant setting on the basis of their known activity in advanced renal cell carcinoma.[1] Axitinib, pazopanib, and sorafenib did not significantly improve the efficacy of adjuvant therapy in randomised phase 3 clinical trials, and sunitinib yielded conflicting results for disease-free survival across randomised phase 3 trials; no overall survival benefit was observed in any of these studies.[2–7] Although adjuvant

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from database inception to March 1, 2022, for articles published in English, using the search strings (no restrictions) "PD-1 OR PD-L1 OR VEGF OR vascular endothelial growth factor OR pembrolizumab OR MK-3475 OR nivolumab OR BMS-936558 OR MPDL3280A OR atezolizumab OR BMS-936559 OR MEDI4736 OR durvalumab OR avelumab OR axitinib OR pazopanib OR sunitinib OR sorafenib AND adjuvant AND renal cell carcinoma" OR "PD-1 OR PD-L1 OR VEGF OR vascular endothelial growth factor OR pembrolizumab OR MK-3475 OR nivolumab OR BMS-936558 OR MPDL3280A OR atezolizumab OR BMS-936559 OR MEDI4736 OR durvalumab OR avelumab OR axitinib OR pazopanib OR sunitinib OR sorafenib AND adjuvant AND RCC." We identified five randomised phase 3 clinical studies of VEGF-targeted therapy (axitinib, pazopanib, sorafenib, and sunitinib) in patients with renal cell carcinoma after nephrectomy. These trials did not show consistent disease-free survival benefit with VEGF inhibition in the adjuvant setting for renal cell carcinoma or any overall survival benefit. We also identified a randomised phase 3 clinical study of durvalumab with or without tremelimumab after nephrectomy for patients with locally advanced renal cell carcinoma (NCT03288532); this study is ongoing and no results have been reported to date. No other reports were identified for results from any other phase 3 clinical studies investigating adjuvant PD-1 or PD-L1 inhibitors (including atezolizumab, avelumab, or nivolumab) for patients with localised renal cell carcinoma after surgery. We thus concluded that there is an unmet clinical need for randomised clinical trial-based evidence for efficacious and tolerable therapies in the adjuvant renal cell carcinoma setting.

Added value of this study

To our knowledge, KEYNOTE-564 is the first randomised phase 3 study to report results for a checkpoint inhibitor as an adjuvant therapy for participants with renal cell carcinoma. On the basis of the protocol-specified first interim analysis of the KEYNOTE-564 trial, pembrolizumab after surgery resulted in a significant improvement in disease-free survival compared with placebo in participants with risk features for disease recurrence. The exploratory analysis after 6 additional months of follow-up reported here supports this benefit, which was consistent across prespecified secondary endpoints and most prespecified and exploratory subgroups. Event numbers for overall survival increased but remained small, and additional follow-up will be needed for robust overall survival analysis. Nevertheless, overall survival data remain consistent with previous findings. No new safety signals were observed with adjuvant pembrolizumab, which had an adverse event profile consistent with previous reports for pembrolizumab monotherapy. Secondary and exploratory analyses showed that pembrolizumab improved the time to progression on next-line therapy and most patients who had progression on placebo were subsequently treated with immune checkpoint inhibition. Masked independent review, which was a secondary endpoint, supported the findings of the initial investigator-assessed analysis.

Implications of all the available evidence

To our knowledge, KEYNOTE-564 is the first positive study for adjuvant immunotherapy in renal cell carcinoma. The efficacy and safety update with 6 additional months of follow-up from the first interim analysis, as well as the spectrum of secondary and exploratory analyses, give further credence to the use of adjuvant pembrolizumab in this population.

sunitinib for renal cell carcinoma was approved for use in the USA, this approval is not supported by strong evidence, and sunitinib is not a globally recommended therapy in this setting. Therefore, most patients with renal cell carcinoma are either placed under clinical surveillance or enter clinical trials after surgery.[8,9]

Patients who are considered disease-free after nephrectomy for renal cell carcinoma are at the highest risk of recurrence during the first 5 years after surgery.[10] Renal cell carcinoma most commonly recurs with distant metastasis, necessitating non-curative systemic first-line treatment.[10–12] Furthermore, specific disease characteristics at diagnosis are associated with an increased risk of recurrence. Primary tumour stage is a known prognostic factor, with up to 26% of patients with stage T2, approximately 50% of patients with stage T3, and nearly all patients with stage T4 disease having a recurrence after nephrectomy.[10,11] Higher tumour nuclear grade and the presence of sarcomatoid features are also independently associated with an increased risk of disease recurrence.[13,14] Patients with localised renal cell carcinoma with one or several high-risk features are in particular need of efficacious adjuvant therapy.

Another group of patients who might benefit from adjuvant therapy are those with resectable soft tissue metastases at diagnosis (M1 stage disease) in addition to the primary renal tumour. Suitable surgical candidates who undergo successful nephrectomy and complete metastasectomy are considered disease free (ie, with no evidence of disease), but remain at high risk of recurrence and death within 5 years after surgery and have no available adjuvant therapeutic options.[10,15–17]

The randomised, double-blind, placebo-controlled, phase 3 KEYNOTE-564 study was designed to investigate adjuvant pembrolizumab monotherapy versus placebo after nephrectomy for participants with localised renal cell carcinoma or after nephrectomy and metastasectomy for participants with M1 stage renal cell carcinoma. The protocol-specified first interim analysis of the study, done after approximately 24 months of follow-up, showed that adjuvant pembrolizumab resulted in a statistically significant and clinically meaningful disease-free survival

benefit compared with placebo in the intention-to-treat population (hazard ratio [HR] 0·68 [95% CI 0·53–0·87]; p=0·002 [two-sided]).[18] Here, we report an updated efficacy and safety analysis of the KEYNOTE-564 study with an additional 6 months of follow-up after the initial analysis, and present the first results from several secondary and exploratory endpoints.

Methods

Study design and participants

KEYNOTE-564 is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial ongoing at 213 hospitals and cancer centres in North America, South America, Europe, Asia, and Australia. Eligible participants were adults aged 18 years or older who had undergone surgery for histologically confirmed renal cell carcinoma with a clear cell component with or without sarcomatoid features. Participants were categorised as having an intermediate-high risk of disease recurrence (pathological tumour stage 2 [pT2] with nuclear grade 4 or sarcomatoid differentiation, no nodal involvement [N0], and no metastasis [M0]; or pT3, any grade, N0, M0), high risk of disease recurrence (pT4, any grade, N0, M0; or any pT, any grade, N+, M0), or M1 stage with no evidence of disease after complete resection of oligometastases synchronously or within 1 year of nephrectomy (M1 with no evidence of disease). Eligible participants had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; had undergone surgery within the 12 weeks before randomisation; had disease-free status at baseline according to investigator assessment; had received no previous systemic therapy for advanced renal cell carcinoma; and provided adequate tissue samples for PD-L1 assessment from the nephrectomy (if they received nephrectomy only), from both the nephrectomy and metastasectomy (if done synchronously), or from the metastasectomy (if done after nephrectomy; nephrectomy tissue sample had to also be provided if available). Participants were excluded if they had any major surgery other than nephrectomy or metastasectomy within the 12 weeks before randomisation; had received previous radiotherapy for renal cell carcinoma; had received previous anti-PD-1, anti-PD-L1, anti-PD-L2, or other coinhibitory T-cell receptor therapy; or had pre-existing brain or bone metastases. Participants with residual disease after nephrectomy were also excluded, in line with US Food and Drug Administration recommendations.[19] Full eligibility criteria are included in the trial protocol in the appendix.

The trial protocol and all amendments were approved by the appropriate ethics committee at each medical centre. This study was done in accordance with Good Clinical Practice standards. All participants provided written, informed consent before enrolment and could withdraw from the trial at any time for any reason if they or a legally acceptable representative withdrew consent.

Randomisation and masking

Participants were enrolled by delegated investigators. The funder randomly assigned participants (1:1) using a permuted block randomisation sequence using SAS version 9.4 with a block size of four to receive pembrolizumab monotherapy or placebo in a double-blind design. Randomisation was done centrally using an interactive voice-response system and interactive web-response system (Almac Clinical Technologies; Souderton, PA, USA) by assigning participants a number that would subsequently identify them for all procedures occurring after randomisation, and that was stratified by metastatic disease status (M0 *vs* M1). The M0 group was further stratified by ECOG performance status (0 *vs* 1) and geographical region (USA *vs* outside the USA). All participants and investigators involved in study treatment administration were masked to the treatment group assignment. Pembrolizumab and placebo were prepared and dispensed in a masked manner by an unmasked pharmacist or qualified trial site personnel.

Procedures

Pembrolizumab 200 mg or placebo were administered intravenously over 30 min once every 3 weeks, up to a maximum of 17 cycles or until a new malignancy or any progression or recurrence of the malignancy under study occurred, the participant or physician decided to discontinue treatment, or any occurrence of pregnancy, intercurrent illness, or recurrent grade 2 or worse pneumonitis. Dose modifications for pembrolizumab were not permitted. Dose interruption was permitted to manage most grade 2 immune-mediated adverse events, and interruption or discontinuation was permitted for grade 3 or 4 immune-mediated adverse events. Study treatment discontinuation was considered permanent, and no retreatment was permitted.

PD-L1 expression in tissue samples was centrally assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies; Carpinteria, CA, USA) by Q² Solutions (Morrisville, NC, USA), and measured using the combined positive score (defined as the number of PD-L1-positive staining cells [tumour cells, lymphocytes, and macrophages] divided by the total number of viable tumour cells, multiplied by 100).

On-trial imaging assessments of the chest, abdomen, and pelvis were done by CT (strongly preferred) or MRI when CT was not available or feasible. Bone imaging was done using bone scintillation or X-ray according to local imaging standards and guidelines. Imaging assessments were done by investigators and site radiologists every 12 weeks in the first 2 years, every 16 weeks in the third to fifth years, and every 24 weeks thereafter until withdrawal of consent, disease recurrence, pregnancy, start of new anticancer treatment, death, or the end of the trial, whichever occurred first. Each participant's recurrence-free status was assessed by the investigator.

Adverse events, serious adverse events, and all other safety events were reported by the participant or appropriate caregiver or legal representative, documented, and proactively followed up by the investigator. Adverse events were collected from the time of randomisation up to 30 days after treatment discontinuation, except for serious adverse events, which were collected up to 90 days after treatment discontinuation. Any serious adverse event reported outside the specified collection period that was considered attributable to study treatment had to be reported to the funder. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Laboratory safety evaluations for haematology (platelet, white blood cell and red blood cell count, red blood cell indices, haemoglobin, and haematocrit), chemistry (albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin, blood urea and nitrogen, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium, and total protein), and urinalysis (specific gravity; glucose, protein, and blood by dipstick; and microscopic examination) were done centrally (at Q² Solutions LLC [Valencia, CA, USA], Q² Solutions Pte Ltd [Singapore], or Q² Solutions Limited [Livingston, UK]) before study treatment administration at each cycle.

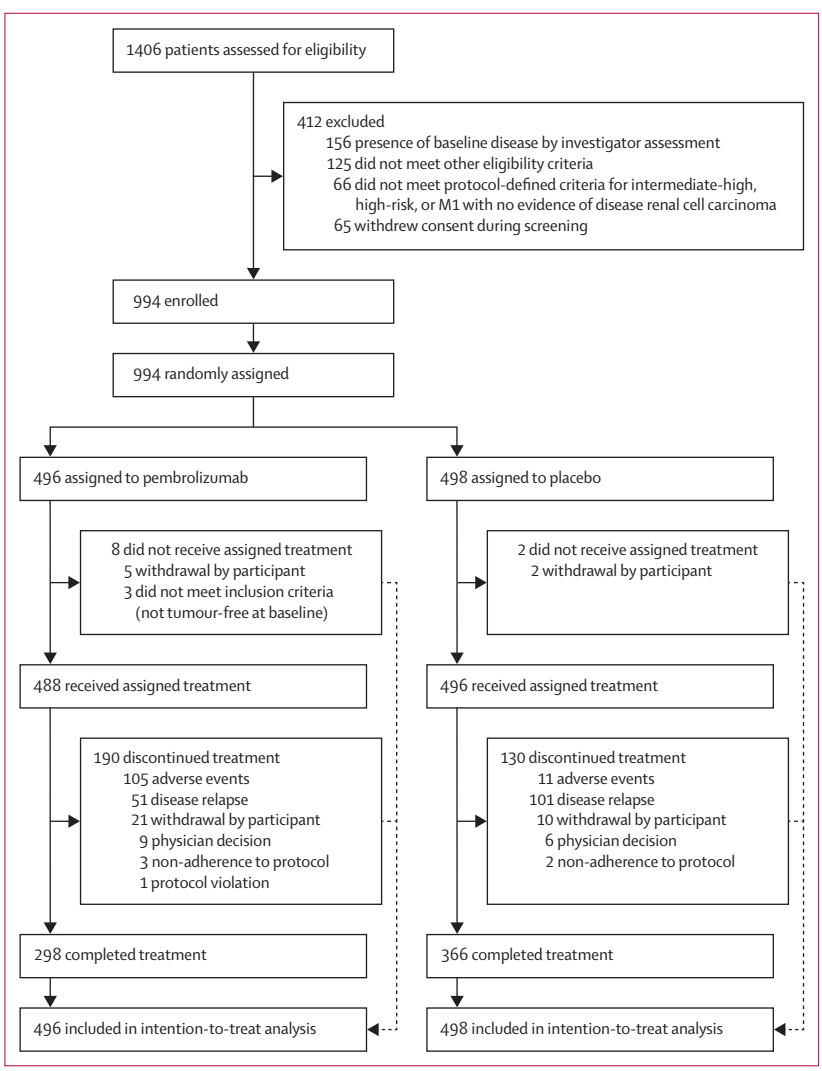

Figure 1: **Trial profile**

Outcomes

The primary endpoint was disease-free survival by investigator assessment, defined as the time from randomisation to the first documented local or distant recurrence of renal cell carcinoma, secondary systemic malignancy, or death from any cause, whichever occurred first. The key secondary endpoint was overall survival, defined as the time from randomisation to death from any cause. Additional secondary endpoints reported here are safety and tolerability, disease-free survival by PD-L1 status (combined positive score <1 *vs* ≥1), disease-free survival by investigator in participants with no evidence of disease by masked independent central review at baseline, event-free survival (defined as the time from randomisation to the first documented local disease recurrence or distant metastases, disease progression, or death, whichever occurred first) by masked independent central review, and disease recurrence-specific survival 1 (defined as the time from randomisation to the first documented local disease recurrence) and 2 (defined as the time from randomisation to the first documented local recurrence with a visceral lesion or distant metastasis with a visceral lesion, whichever occurred first) by investigator assessment.

The following secondary and exploratory endpoints will be reported separately or as applicable with additional study follow-up: overall survival by PD-L1 status (combined positive score <1 *vs* ≥1), pharmacokinetics and antidrug antibodies, biomarkers, and patient-reported outcomes. The secondary endpoints of health-related quality of life and physical functioning by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire and disease symptoms by the Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms tools were previously published for the protocol-specified first interim analysis of the study (with a data cutoff date of Dec 14, 2020).[18,20]

Statistical analysis

We planned to enrol approximately 990 eligible participants, with 495 participants assigned to each group. The sample size was calculated to ensure 95% power to detect disease-free survival superiority for adjuvant pembrolizumab versus placebo at an initially assigned α of 2·5% (one-sided) at an HR of 0·67 for the intention-to-treat population (defined as all randomly assigned participants), with an assumed proportion of cured participants of 0·3 based on a Poisson mixture cure-rate model. Three interim analyses were planned.

	Pembrolizumab (n=496)	Placebo (n=498)
Age, years		
Median (IQR)	60 (51–66)	60 (52–67)
<65	338 (68%)	326 (65%)
Sex		
Male	347 (70%)	359 (72%)
Female	149 (30%)	139 (28%)
ECOG performance status score		
0	421 (85%)	426 (86%)
1	75 (15%)	72 (14%)
Geographical location		
North America	133 (27%)	125 (25%)
EU*	188 (38%)	187 (38%)
Rest of the world	175 (35%)	186 (37%)
Ethnicity		
Hispanic or Latinx	72 (14%)	62 (12%)
Non-Hispanic or Latinx	381 (77%)	394 (79%)
Not reported	21 (4%)	20 (4%)
Missing or unknown	22 (4%)	22 (4%)
Type of nephrectomy		
Partial	37 (7%)	38 (8%)
Radical	459 (93%)	460 (92%)
Primary tumour stage		
T1	11 (2%)	15 (3%)
T2	27 (5%)	33 (7%)
T3	444 (90%)	437 (88%)
T4	14 (3%)	13 (3%)
Tumour nuclear grade		
1	19 (4%)	16 (3%)
2	153 (31%)	150 (30%)
3	219 (44%)	213 (43%)
4	103 (21%)	119 (24%)
Missing	2 (<1%)	0
(Continued from previous column)		
Lymph node stage		
N0	465 (94%)	467 (94%)
N1	31 (6%)	31 (6%)
Metastatic stage		
M0	467 (94%)	469 (94%)
M1 with no evidence of disease	29 (6%)	29 (6%)
Disease risk category		
M0 intermediate to high	427 (86%)†	433 (87%)
M0 high	40 (8%)	36 (7%)
M1 with no evidence of disease	29 (6%)	29 (6%)
Sarcomatoid features		
Present	52 (10%)	59 (12%)
Absent	414 (83%)	415 (83%)
Unknown	30 (6%)	24 (5%)
PD-L1 combined positive score†		
<1	124 (25%)	113 (23%)
≥1	365 (74%)	383 (77%)
Missing	7 (1%)	2 (<1%)

Data n (%), unless otherwise indicated. The intention-to-treat population included all randomly assigned participants. ECOG=Eastern Cooperative Oncology Group. *Includes the UK as they were still a part of the EU at the start of the study. †Included five participants with T2, grade ≤3, N0, M0 or T1, N0, or M0 who were excluded from the analysis (protocol violations). †PD-L1 combined positive score was calculated as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) divided by the total number of tumour cells, multiplied by 100.

Table 1: **Baseline demographic and clinical characteristics in the intention-to-treat population**

The first analysis occurred after 260 disease-free survival events by investigator assessment and a minimum follow-up (defined as the time from random assignment of the last participant to the first interim analysis data cutoff date) of 15 months for the intention-to-treat population.[18] The present analysis is an updated analysis as agreed with, and requested by, regulatory agencies to provide an additional 6 months of follow-up data after the first interim analysis. The type I error rate was strongly controlled at 2·5% by the graphical Maurer and Bretz approach.[21] Disease-free survival was tested first, with the α passed to the analysis of overall survival if the null hypothesis of disease-free survival was rejected. Because the primary endpoint of disease-free survival was met in the protocol-specified first analysis,[18] no α was allocated and no formal statistical testing was done for disease-free survival in this updated analysis.

The statistical hypothesis testing boundary for overall survival was set at 0·000095 based on the Lan-DeMets O'Brien-Fleming spending function.[22] The null hypothesis of overall survival was rejected if the one-sided p-value of the between-group comparison was less than the p value boundary. Subsequent interim analyses are planned on the basis of prespecified event accruals for overall survival. The final analysis for overall survival is planned to occur after approximately 200 overall survival events.

Efficacy was assessed in the intention-to-treat population using the Kaplan-Meier method. The survival rates at month 30 and their 95% CIs were estimated using the Kaplan-Meier method. Safety was assessed in the population of all participants as-treated, comprising all participants who received at least one dose of pembrolizumab or placebo in the study. HRs and nominal 95% CIs were estimated with a stratified Cox proportional-hazard model with Efron's method of tie handling and with trial group as a covariate. Between-group differences were assessed by means of a stratified log-rank test. The stratification factors used for randomisation were applied to the Cox model. Disease-free survival was analysed in prespecified subgroups (ECOG performance status, metastatic status, age, sex, geographical region, type of nephrectomy, and PD-L1 combined positive score) and prespecified exploratory subgroups (protocol-specified recurrence risk, presence

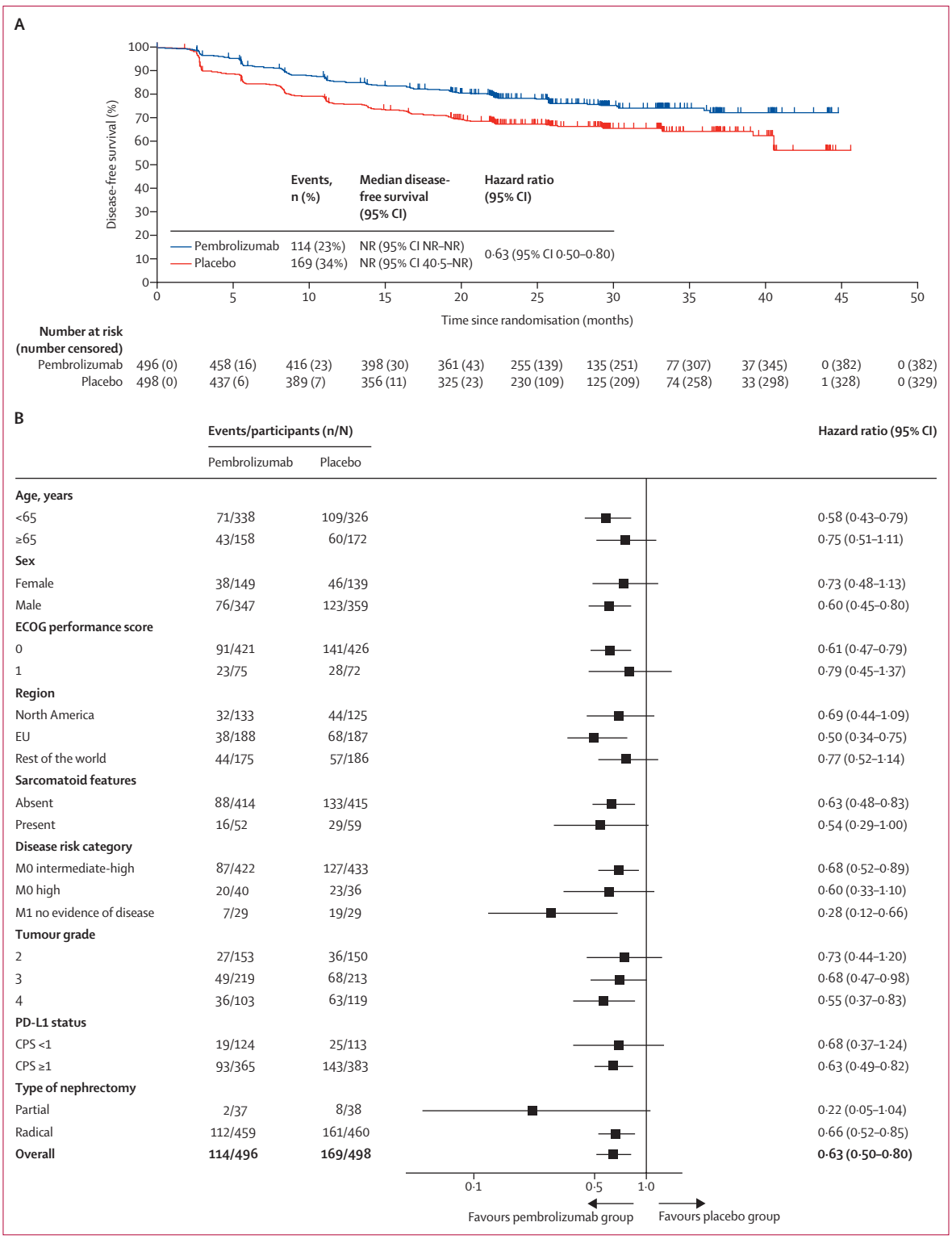

Figure 2: **Kaplan-Meier estimates of disease-free survival (primary endpoint) for the overall population (A) and subgroup analysis of disease-free survival (B)** Disease-free survival by investigator review in all randomly assigned participants and subgroup analysis of disease-free survival. Tick marks in the Kaplan-Meier plot show censoring of the data at the last time the participant was known to be alive and recurrence-free. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. NR=not reached.

of sarcomatoid features, and tumour nuclear grade) using an unstratified Cox model. The non-parametric cumulative incidence estimator was used to estimate the disease recurrence-specific survival 1 and 2 curves in each treatment group. For disease recurrence-specific survival 1, distant disease recurrence and death were competing risk events. For disease recurrence-specific survival 2, death, local recurrence without visceral lesion, and distant metastasis without visceral lesion were competing risk events. No formal treatment comparisons were planned with respect to safety results.

Post-hoc exploratory endpoints reported here are distant metastasis-free survival (defined as the time to radiographically detectable metastatic disease or any-cause death), time to first subsequent therapy or any-cause death, progression-free survival 2 (defined as time from randomisation to progression on next line therapy or any-cause death), time to treatment discontinuation from adverse events, and time to first onset of treatment-related adverse events. Post-hoc landmark analyses at 30 months were done for disease-free survival, overall survival, event-free survival, distant metastasis-free survival, and progression-free survival 2.

An independent, external data monitoring committee monitored safety and efficacy during the study and made recommendations about the overall risk and benefit to trial participants. SAS version 9.4 was used for all statistical analyses. This trial is registered with ClinicalTrials.gov, NCT03142334.

Role of the funding source

The funder of the study contributed to the study design, data collection, data analysis, and data interpretation in collaboration with the authors, and provided financial support for editorial and writing assistance. Investigators and site personnel collected data, which was housed on the Merck & Co, Inc, Rahway, NJ, USA database.

Results

1406 participants were screened for this study, of whom 412 were excluded (figure 1). Between June 30, 2017, and Sept 20, 2019, 994 enrolled participants were randomly assigned to receive adjuvant pembrolizumab (496 participants) or placebo (498 participants; figure 1) and were assessed for the primary endpoint of disease-free survival. Participant demographics and baseline disease characteristics were generally balanced across the two study groups (table 1).

At this updated analysis, median follow-up (time from randomisation to the data cutoff date of June 14, 2021) was 30·1 months (IQR 25·7–36·7). The median number of treatment cycles administered was 17 (IQR 9–17) in the pembrolizumab group and 17 (16–17) in the placebo group. Among participants who received at least one dose of study treatment, 298 (61%) of 488 in the pembrolizumab group and 366 (74%) of 496 in the placebo group completed all 17 planned cycles of treatment. The most common reason for discontinuation of study treatment was an adverse event (105 [22%] of 488 participants in the pembrolizumab group *vs* 11 [2%] of 496 in the placebo group) and disease recurrence (51 [10%] of 488 participants in the pembrolizumab group *vs* 101 [20%] of 496 participants) in the placebo group. No participants remained on study therapy at the time of data cutoff.

Disease-free survival was better with pembrolizumab compared with placebo (HR 0·63 [95% CI 0·50–0·80]) in the intention-to-treat population (figure 2A); median disease-free survival was not reached in either group. At 30 months (post-hoc analysis), the estimated proportion of participants who remained alive and recurrence-free was 75·2% (95% CI 70·8–79·1) in the pembrolizumab group and 65·5% (60·9–69·7) in the placebo group.

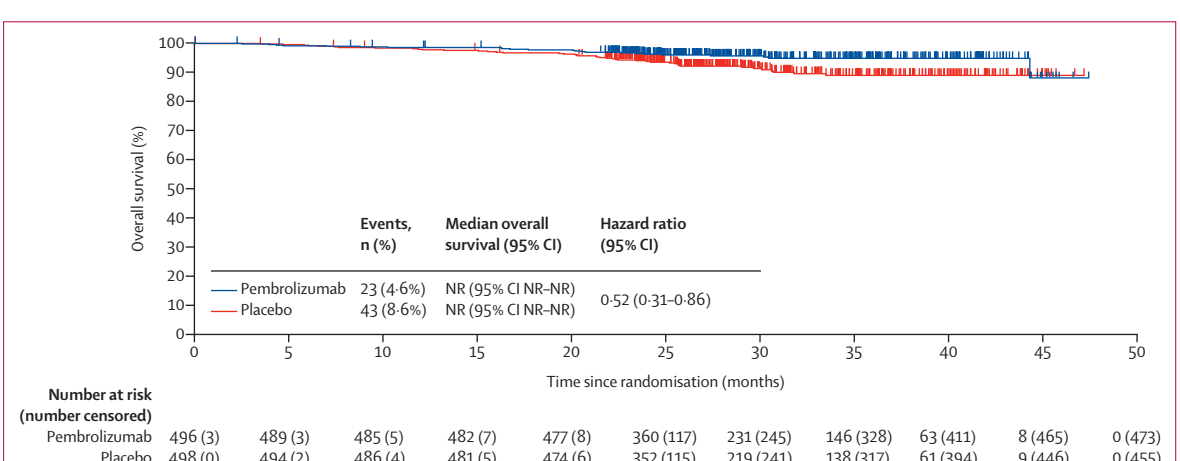

Figure 3: **Kaplan-Meier estimate of overall survival**
Overall survival (key secondary endpoint) was assessed in all randomly assigned participants. Tick marks in the Kaplan-Meier plot show censoring of the data at the last time the participant was known to be alive. NR=not reached.

	Pembrolizumab (n=488)			Placebo (n=496)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fatigue	95 (19%)	4 (1%)	0	71 (14%)	0	0
Pruritus	90 (18%)	1 (<1%)	0	57 (11%)	0	0
Hypothyroidism	84 (17%)	1 (<1%)	0	13 (3%)	0	0
Diarrhoea	69 (14%)	8 (2%)	0	51 (10%)	0	0
Rash	69 (14%)	4 (1%)	0	36 (7%)	0	0
Hyperthyroidism	52 (11%)	1 (<1%)	0	0	0	0
Arthralgia	44 (9%)	1 (<1%)	0	43 (9%)	0	0
Myalgia	29 (6%)	1 (<1%)	0	20 (4%)	0	0
Asthenia	27 (6%)	1 (<1%)	0	23 (5%)	0	0
Increased alanine aminotransferase	13 (3%)	9 (2%)	0	8 (2%)	1 (<1%)	0
Increased aspartate aminotransferase	16 (3%)	6 (1%)	0	5 (1%)	0	0
Dry mouth	19 (4%)	1 (<1%)	0	1 (<1%)	0	0
Increased blood creatine	19 (4%)	1 (<1%)	0	10 (2%)	0	0
Maculopapular rash	17 (3%)	2 (<1%)	0	6 (1%)	0	0
Decreased appetite	14 (3%)	1 (<1%)	0	2 (<1%)	0	0
Adrenal insufficiency	4 (1%)	6 (1%)	0	0	0	0
Vomiting	9 (2%)	1 (<1%)	0	3 (1%)	0	0
Pyrexia	8 (2%)	1 (<1%)	0	2 (<1%)	0	0
Colitis	3 (1%)	5 (1%)	0	1 (<1%)	0	0
Pneumonitis	6 (1%)	1 (<1%)	1 (<1%)	3 (1%)	0	0
Arthritis	6 (1%)	1 (<1%)	0	3 (1%)	0	0
Increased blood alkaline phosphatase	6 (1%)	1 (<1%)	0	1 (<1%)	0	0
Increased amylase	4 (1%)	2 (<1%)	0	4 (1%)	0	0
Increased γ-glutamyltransferase	3 (1%)	1 (<1%)	2 (<1%)	0	0	0
Diabetic ketoacidosis	0	4 (1%)	1 (<1%)	0	0	0
Hyperglycaemia	2 (<1%)	2 (<1%)	1 (<1%)	3 (1%)	1 (<1%)	0
Hypophosphataemia	4 (1%)	1 (<1%)	0	4 (1%)	0	0
Increased lipase	3 (1%)	1 (<1%)	1 (<1%)	4 (1%)	0	0
Infusion-related reaction	4 (1%)	1 (<1%)	0	4 (1%)	0	0
Increased transaminases	4 (1%)	1 (<1%)	0	2 (<1%)	0	0
Thyroiditis	4 (1%)	1 (<1%)	0	1 (<1%)	0	0
Type 1 diabetes	1 (<1%)	3 (1%)	1 (<1%)	0	0	0
Acute kidney injury	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0
Hypertension	1 (<1%)	3 (1%)	0	5 (1%)	1 (<1%)	0
Diabetes	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Liver disorder	2 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Neutropenia	2 (<1%)	1 (<1%)	0	2 (<1%)	0	0
Sjögren's syndrome	2 (<1%)	1 (<1%)	0	0	0	0
Aseptic meningitis	0	2 (<1%)	0	0	0	0
Asthma	1 (<1%)	1 (<1%)	0	0	0	0
Cholestasis	1 (<1%)	0	1 (<1%)	0	0	0
Hepatitis	0	2 (<1%)	0	0	0	0
Hypersensitivity	1 (<1%)	1 (<1%)	0	0	0	0
Hypophysitis	0	2 (<1%)	0	0	0	0
Immune-mediated lung disease	1 (<1%)	0	1 (<1%)	0	0	0
Lichen planus	1 (<1%)	1 (<1%)	0	0	0	0
Myocardial infarction	0	1 (<1%)	1 (<1%)	0	0	0
Pulmonary embolism	1 (<1%)	1 (<1%)	0	0	0	0
Anorectal infection	0	1 (<1%)	0	0	0	0

(Table 2 continues on next page)

Disease-free survival with adjuvant pembrolizumab versus placebo in prespecified and exploratory participant subgroups is shown in figure 2B and appendix pp 14–18.

Point estimates of the disease-free survival HR were below 1·0 regardless of PD-L1 status (figure 2B). Median disease-free survival was not reached for either group, although the number of events was small.

66 deaths occurred in the intention-to-treat population (23 [5%] of 496 participants in the pembrolizumab group and 43 [9%] of 498 participants in the placebo group). Overall survival was better with pembrolizumab compared with placebo (HR 0·52 [nominal 95% CI 0·31–0·86]; figure 3). Median overall survival was not reached in either group. At 30 months, the estimated proportion of participants who were alive was 95·7% (95% CI 93·3–97·2) in the pembrolizumab group and 91·4% (88·3–93·7) in the placebo group. The p value did not cross the one-sided p value boundary of 0·000095, and no statistical significance claim can be made. Because only 33% of death events needed for the final overall survival analysis had accrued by the data cutoff date (66 of 200 events), additional follow-up is needed for overall survival.

For participants with no evidence of disease by masked independent central review at baseline the HR for progression or death was 0·67 (95% CI 0·52–0·86; appendix p 21). Median disease-free survival was not reached for the pembrolizumab group (95% CI not reached to not reached) or placebo group (95% CI 40·5 to not reached). Event-free survival by masked independent central review also favoured pembrolizumab versus placebo (HR 0·75, 95% CI 0·60–0·95). 133 (27%) events in the pembrolizumab group and 167 (34%) events in the placebo group occurred. Median event-free survival was not reached in either group (appendix p 22). At 30 months (post-hoc analysis), the estimated proportion of participants who were alive and had not had an event was 70·6% (95% CI 65·9–74·7) in the pembrolizumab group and 64·8% (60·2–69·0) in the placebo group.

The analysis of time to local recurrence (disease recurrence-specific survival 1) showed 18 (4%) events (local renal cell carcinoma recurrence) in the pembrolizumab group and 35 (7%) events in the placebo group. At 30 months, the cumulative incidence of events was 3·8% (95% CI 2·3–6·0) in the pembrolizumab group and 7·6% (5·3–10·3) in the placebo group (appendix p 23). The analysis of time to visceral recurrence or distant metastasis (disease recurrence-specific survival 2) showed 100 (20%) events (local recurrence with visceral lesion or distant kidney cancer metastases with visceral lesion) in the pembrolizumab group compared with 149 (30%) in the placebo group (appendix p 23). At 30 months, the cumulative incidence of events was 21·4% (95% CI 17·6–25·4) in the pembrolizumab group and 30·5% (26·4–34·8) in the placebo group.

Of the 108 (22%) observed recurrence events in the pembrolizumab group, 13 (12%) were categorised as local recurrences only, 90 (83%) were distant metastasis

only, and five (5%) included both local and distant metastasis (appendix p 8). Of the 166 (33%) observed recurrence events in the placebo group, 26 (16%) were local recurrences only, 131 (79%) were distant metastasis only, and nine (5%) included both local and distant metastasis. Distant metastasis-free survival favoured pembrolizumab over placebo (HR 0·63 [95% CI 0·49–0·82]; post-hoc analysis; appendix p 20). At 30 months (post-hoc analysis), the estimated proportion of participants who were alive without distant metastasis was 77·3% (95% CI 73·0–81·0) in the pembrolizumab group and 68·8% (64·4–72·9) in the placebo group.

Overall, 67 (14%) of 496 participants in the pembrolizumab group and 99 (20%) of 498 participants in the placebo group received at least one line of subsequent anticancer drug therapy after disease recurrence. 60 (12%) participants in the pembrolizumab group and 85 (17%) participants in the placebo group received subsequent VEGF-targeted or VEGF receptor-targeted therapy. 16 (3%) participants in the pembrolizumab group and 59 (12%) participants in the placebo group received subsequent anti–PD-1 or anti-PD-L1 therapy (appendix p 9). Time to first subsequent therapy or any-cause death was longer in the pembrolizumab group than in the placebo group (HR 0·67 [95% CI 0·50–0·90]; post-hoc analysis). The median time to first subsequent therapy or any-cause death was not reached for either group. 77 events were observed in the pembrolizumab group (10 participants died and 67 began subsequent drug therapy) and 110 events were observed in the placebo group (11 participants died and 99 began subsequent drug therapy). At 30 months (post-hoc analysis), the estimated proportion of participants who were alive and did not begin subsequent therapy with an anticancer drug was 85·4% (95% CI 81·9–88·3) in the pembrolizumab group and 77·8% (73·8–81·3) in the placebo group.

The HR for progression or death on next-line therapy (progression-free survival 2) was 0·57 (95% CI 0·39–0·85) in the intention-to-treat population (post-hoc analysis; appendix p 19). Median progression-free survival 2 was not reached for either study group. 40 events were observed in the pembrolizumab group (12 deaths and 28 progressions) and 68 events were observed in the placebo group (14 deaths and 54 progressions). At 30 months (post-hoc analysis), the estimated proportion of participants who were alive without disease progression on next-line therapy was 92·5% (95% CI 89·7–94·5) in the pembrolizumab group and 86·1% (82·5–89·1) in the placebo group.

The adverse event profile of pembrolizumab was in line with those reported for this study previously,[18] with no new safety signals (table 2). In the safety population (n=488 in the pembrolizumab group and n=496 in the placebo group), the median duration of treatment was 11·1 months (IQR 6·2–11·3) in the pembrolizumab group and 11·1 months (10·5–11·3) in the placebo group. The median time to first onset of treatment-related adverse events occurring in at least 5% of participants was less than 6 months from treatment initiation (post hoc; appendix p 24). Grade 3 or worse adverse events of any cause were reported in 157 (32%) of 488 participants in the pembrolizumab group and 88 (18%) of 496 participants in the placebo group (appendix p 10). The most common grade 3 or worse adverse events of any cause were hypertension (in 14 [3%] participants) and increased alanine aminotransferase (11 [2%] participants) in the pembrolizumab group and hypertension (13 [3%] participants) in the placebo group. Adverse events leading to treatment discontinuation occurred in 103 (21%) of 488 participants in the pembrolizumab group and 11 (2%) of 496 participants in the placebo group (appendix p 11). The most common events (≥1% incidence) leading to discontinuation of pembrolizumab were increased alanine aminotransferase (eight [2%] participants), adrenal insufficiency (six [1%]), and colitis (five [1%]). The median time to treatment discontinuation because of

	Pembrolizumab (n=488)			Placebo (n=496)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Atrial fibrillation	0	1 (<1%)	0	0	0	0
Autoimmune thyroiditis	0	1 (<1%)	0	0	0	0
Cardiac failure	0	0	1 (<1%)	0	0	0
Cerebellar syndrome	0	1 (<1%)	0	0	0	0
Chronic kidney disease	0	1 (<1%)	0	0	0	0
Drug-induced liver injury	0	1 (<1%)	0	0	0	0
Enterocolitis	0	1 (<1%)	0	0	0	0
Facial paralysis	0	1 (<1%)	0	0	0	0
Glucocorticoid deficiency	0	1 (<1%)	0	0	0	0
Hepatotoxicity	0	1 (<1%)	0	0	1 (<1%)	0
Hyperlipasaemia	0	0	0	0	1 (<1%)	0
Hypertriglyceridaemia	0	1 (<1%)	0	0	0	0
Hyponatraemia	1 (<1%)	0	0	0	1 (<1%)	0
Immune-mediated hepatitis	0	1 (<1%)	0	0	0	0
Immune thrombocytopenia	0	1 (<1%)	0	0	0	0
Impaired glucose tolerance	0	0	1 (<1%)	0	0	0
Increased blood creatine phosphokinase	0	1 (<1%)	0	1 (<1%)	0	0
Increased blood triglycerides	0	1 (<1%)	0	0	0	0
Interstitial lung disease	0	1 (<1%)	0	0	0	0
Lichenification	0	1 (<1%)	0	0	0	0
Myocarditis	0	1 (<1%)	0	0	0	0
Pleuropericarditis	0	1 (<1%)	0	0	0	0
Stevens-Johnson syndrome	0	1 (<1%)	0	0	0	0
Thrombocytopenia	0	0	1 (<1%)	2 (<1%)	0	0
Tubulointerstitial nephritis	0	1 (<1%)	0	0	0	0

Data are n (%). The safety population includes all participants who received at least one dose of trial treatment. Adverse events are presented according to the Medical Dictionary for Regulatory Affairs system organ class. Numbers represent highest toxicity grade (ie, each participant is counted only once in each row). Grade 1 or 2 events occurring in at least 10% of the population and all grade 3 or 4 events are shown. No grade 5 treatment-related adverse events occurred in either group.

Table 2: **Treatment-related adverse events in the safety population**

adverse events was 4·1 months (IQR 1·4–7·1) in the pembrolizumab group and 4·9 months (2·1–10·6) for the placebo group (post-hoc analysis). As reported previously,[18] two deaths from an adverse event were reported in the pembrolizumab group (one each from pneumonia and multiple organ dysfunction syndrome), and one death occurred in the placebo group (from intracranial haemorrhage); no new deaths have occurred since the initial analysis.

No deaths from treatment-related adverse events occurred in either study group. Serious adverse events attributed to study treatment occurred in 59 (12%) participants in the pembrolizumab group and one (<1%) participant in the placebo group (appendix p 12). The most common serious treatment-related adverse events (≥1% incidence) in the pembrolizumab group were adrenal insufficiency (six [1%] participants), colitis (six [1%]), and diabetic ketoacidosis (five [1%]).

Immune-mediated adverse events, regardless of attribution to study treatment, occurred in 174 (36%) participants in the pembrolizumab group and 34 (7%) participants in the placebo group (appendix p 13). The most common immune-mediated adverse events were hypothyroidism (103 [21%] participants) and hyperthyroidism (62 [13%]) in the pembrolizumab group and hypothyroidism (18 [4%] participants) in the placebo group. High-dose systemic corticosteroid treatment (defined as ≥40 mg per day) for immune-mediated adverse events was administered to 37 (8%) participants in the pembrolizumab group and three (1%) participants in the placebo group.

Discussion

In this updated analysis after 30 months of follow-up, adjuvant pembrolizumab continued to show a benefit in disease-free survival compared with placebo after surgery for renal cell carcinoma. The estimated proportion of participants who were alive and recurrence free was approximately 10% higher with pembrolizumab versus placebo and was consistent over time. Disease-free survival benefit with pembrolizumab versus placebo was also observed across several prespecified and exploratory subgroups, consistently with the findings for the intention-to-treat population. Subgroup analyses showed benefit irrespective of the presence of sarcomatoid features, nuclear tumour grade 4, or M1 with no evidence of disease status at baseline, although the numbers in some subgroups were small and should be interpreted with caution. Analysis of disease-free survival showed a consistent advantage for pembrolizumab, supporting the findings of the first interim analysis. Point estimates of the disease-free survival were below 1·0 regardless of PD-L1 status. A large proportion of participants in KEYNOTE-564 were classified as having tumours that expressed PD-L1, which probably reflects the assay used (staining of immune and tumour cells) rather than unique features within this study population.

In the absence of mature overall survival data (only 33% of events needed for final analysis were accrued by the data cutoff date), progression-free survival 2 and time to subsequent therapy are important predefined intermediate endpoints in clinical trials, serving as possible surrogates for overall survival.[23,24] Pembrolizumab delayed time to subsequent therapy and improved progression-free survival 2 compared with placebo. Additionally, fewer participants treated with pembrolizumab received subsequent therapy than did those treated with placebo. Among participants who had a recurrence event, most presented with distant metastasis at relapse in both groups.[10–12] Furthermore, pembrolizumab improved distant metastasis-free survival compared with placebo. The delay in time to treatment failure for advanced disease supports the hypothesis that these patients might not be rescued by first-line treatment for advanced disease.

The safety profile of adjuvant pembrolizumab remained consistent with the primary findings of the study. No notable increase in the use of high-dose steroids after treatment discontinuation or completion was observed in this updated analysis.[18] Although pembrolizumab was well tolerated, management of adverse events is an important consideration. Patient counselling around risks and benefits of adjuvant pembrolizumab should occur before starting therapy.

A limitation of the current analysis is that overall survival data were immature, and planned analyses are pending. Additional follow-up is needed to address this key secondary endpoint; the Lan-DeMets O'Brien-Fleming spending function reserves larger α for analysis at later timepoints.[22] This analysis was requested by regulatory agencies and comes only 6 months after the initial analysis. Alpha allocation for overall survival was low and was unlikely to be significantly different from the initial analysis.

To our knowledge, the KEYNOTE-564 study is the first randomised phase 3 study to report positive results for adjuvant immunotherapy for participants with renal cell carcinoma. Additional follow-up and analyses reaffirmed the significant disease-free survival benefit observed in our previous analysis and supported adjuvant pembrolizumab as a potential new standard of care for patients with renal cell carcinoma with an increased risk of disease recurrence after surgery.

Contributors

TKC, KI, DIQ, and TP conceived, designed, or planned the study. LX analysed the data. TKC, PT, SHP, BV, TF, SNS, JH, Y-HC, HG, JLL, NS, AT-V, MG-G, MM, NBH, PS, DIQ, and TP acquired the data. TKC, SNS, AT-V, JEB, KI, DIQ, and TP helped interpret the results. TKC, JEB, LX, KI, and TP drafted the manuscript. All authors had full access to and verified the underlying data. All authors revised and reviewed this work and had final approval of the submitted manuscript for publication. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

TP reports having served as a consultant or adviser for Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Eisai, Exelixis, Incyte, Ipsen, Johnson & Johnson, Merck, Merck Serono, MSD, Novartis, Pfizer, Roche, and

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DIQ reports having served as a consultant or adviser for Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Exelixis, Genentech/Roche, Janssen Oncology, MSD, Myovant Sciences, Novartis, Pfizer, Seattle Genetics, and US Biotest; honoraria from Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Exelixis, Genentech/Roche, MSD, Myovant Sciences, Novartis, Pfizer, and Seattle Genetics; research funding paid to institution from Genentech/Roche, Merck, and Pfizer; and travel, accommodations, and expenses from Astellas Pharma, Bayer, Bristol Myers Squibb Japan, Exelexis, Merck, and Roche. 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All other authors declare no competing interests.

Data sharing

Merck Sharp & Dohme LLC (MSD), a subsidiary of Merck & Co, Inc, Rahway, NJ, USA, is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of 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 (http://engagezone.msd.com/ds_documentation.php) 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 USA and EU or after product development is discontinued. Some circumstances that might prevent MSD from sharing requested data, including country-specific or region-specific regulations. If the request is declined, the decision 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.

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