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ABSTRACT

BACKGROUND

Patients with renal-cell carcinoma who undergo nephrectomy have no options for adjuvant therapy to reduce the risk of recurrence that have high levels of supporting evidence.

METHODS

In a double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with clear-cell renal-cell carcinoma who were at high risk for recurrence after nephrectomy, with or without metastasectomy, to receive either adjuvant pembrolizumab (at a dose of 200 mg) or placebo intravenously once every 3 weeks for up to 17 cycles (approximately 1 year). The primary end point was disease-free survival according to the investigator's assessment. Overall survival was a key secondary end point. Safety was a secondary end point.

RESULTS

A total of 496 patients were randomly assigned to receive pembrolizumab, and 498 to receive placebo. At the prespecified interim analysis, the median time from randomization to the data-cutoff date was 24.1 months. Pembrolizumab therapy was associated with significantly longer disease-free survival than placebo (disease-free survival at 24 months, 77.3% vs. 68.1%; hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P=0.002 [two-sided]). The estimated percentage of patients who remained alive at 24 months was 96.6% in the pembrolizumab group and 93.5% in the placebo group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96). Grade 3 or higher adverse events of any cause occurred in 32.4% of the patients who received pembrolizumab and in 17.7% of those who received placebo. No deaths related to pembrolizumab therapy occurred.

CONCLUSIONS

Pembrolizumab treatment led to a significant improvement in disease-free survival as compared with placebo after surgery among patients with kidney cancer who were at high risk for recurrence. (Funded by Merck Sharp and Dohme, a subsidiary of Merck; KEYNOTE-564 ClinicalTrials.gov number, NCT03142334.)

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*A full list of the KEYNOTE-564 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Partial or radical nephrectomy is the standard-of-care treatment for locoregional clear-cell renal-cell carcinoma.[1,2] Nevertheless, nearly half the patients will eventually have disease recurrence after surgery, with most of these patients having distant metastases, leading to a substantially shortened life expectancy.[3] Risk factors such as disease stage, size, nuclear grade, and regional lymph-node involvement of the resected tumor are associated with an increased likelihood of disease recurrence, as well as with a reduced duration of recurrence- and metastasis-free survival.[2,4-8] Surgery also has a role in the treatment of a highly selected group of patients with advanced renal-cell carcinoma (M1 stage, indicating metastasis in a distant organ or tissue) with surgically resectable oligometastatic sites. After nephrectomy and metastasectomy, this disease status is termed "M1 with no evidence of disease" (M1 NED, defined as resection of the primary tumor and solid, isolated, soft-tissue metastases). Patients with M1 NED status are also at high risk for disease recurrence.[5,9]

There is no globally accepted standard adjuvant therapy that has been supported by high levels of evidence for patients with renal-cell carcinoma after surgery. Current treatment guidelines recommend entry into a clinical trial or active surveillance after surgery.[1,2] Despite the known role of angiogenesis in renal-cell carcinoma and the established antitumor activity of vascular endothelial growth factor (VEGF)–targeted therapy in the context of advanced disease, adjuvant therapy with axitinib, pazopanib, sorafenib, and sunitinib has generally failed to substantially improve disease-free survival outcomes in randomized phase 3 trials, including in the double-blind, three-group Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial of sunitinib or sorafenib as compared with placebo.[10-14] However, the Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy (S-TRAC) trial showed a significant result for disease-free survival (primary end point) with sunitinib as compared with placebo.[15] As a result, sunitinib is approved for adjuvant use in the United States.[1] However, owing to the associated adverse-event profile and conflicting conclusions of the S-TRAC and ASSURE trials regarding overall benefit, adjuvant therapy with sunitinib is not approved in other parts of the world, such as the European Union.[2,10,15] Therefore, adjuvant-therapy use in patients with renal-cell carcinoma after nephrectomy is limited owing to a dearth of evidence in support of currently available options.

Anti–programmed death 1 (PD-1) antibodies such as pembrolizumab have shown activity as monotherapy and in combination with other agents in patients with advanced renal-cell carcinoma[16-25] and thus may present a potential adjuvant strategy for treating this disease. We conducted the KEYNOTE-564 trial to evaluate whether treatment with pembrolizumab after nephrectomy, with or without metastasectomy, would result in improved outcomes, as compared with placebo, in patients with clear-cell renal-cell carcinoma and an intermediate-to-high or high risk of recurrence or M1 NED status.

Methods

Patients

Eligible patients were at least 18 years of age and had histologically confirmed locoregional renal-cell carcinoma with a clear-cell component and met protocol-defined criteria for a high risk of recurrence (i.e., tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph-node metastasis, or stage M1 with NED), adapted from previous clinical research, published literature, and previous trials of adjuvant therapy.[3,8,26-28] Patients could not have received any previous systemic therapy for renal-cell carcinoma and must have undergone surgery (partial or radical nephrectomy or metastasectomy) with negative surgical margins within 12 weeks before randomization. In the case of patients with M1 NED status, M1 disease was present in addition to the primary tumor at diagnosis, and metastases had to be completely resected at the time of nephrectomy or within 1 year after nephrectomy. Disease-free status at baseline was assessed by the investigator. Additional eligibility criteria are listed in the Methods section in the Supplementary Appendix and in sections 6.1 and 6.2 in the trial protocol, both of which are available with the full text of this article at NEJM.org.

Trial Design and Interventions

In this phase 3, randomized, double-blind, international trial, patients were randomly assigned in a 1:1 ratio to receive adjuvant pembrolizumab

or placebo after nephrectomy, with or without metastasectomy. Randomization was stratified according to metastatic status on the basis of the investigator's review (M0 [no metastasis] vs. M1 NED). Within the M0 subgroup, randomization was further stratified according to the Eastern Cooperative Oncology Group performance-status score (0 vs. 1; scores range from 0 to 5, with higher scores indicating greater disability) and geographic location (United States vs. outside the United States). The patients and investigators were both unaware of the group assignment.

Pembrolizumab (at a dose of 200 mg) or placebo (carrier saline) was administered intravenously once every 3 weeks for a maximum of 17 cycles (approximately 1 year) or until disease recurrence, unacceptable toxic effects, intercurrent illness preventing further administration of pembrolizumab or placebo, decision by the investigator, a new cancer resulting in active treatment, pregnancy, or nonadherence to the protocol. The interruption or discontinuation, but not dose modification, of pembrolizumab was permitted. Guidelines regarding the interruption of the full dose or discontinuation of pembrolizumab or placebo are outlined in sections 7.2 and 8.1 in the protocol.

END POINTS AND ASSESSMENTS

The primary end point was disease-free survival, which was defined as the time from randomization to the first documented local or distant recurrence of renal-cell carcinoma or death due to any cause, whichever occurred first, as assessed by the investigator. Overall survival, which was defined as the time from randomization to death due to any cause, was a key secondary end point. Safety and patient-reported outcomes were secondary end points. The full list of trial objectives is provided in section 4 in the protocol.

Efficacy was assessed by the investigators in the intention-to-treat population, which included all the patients who underwent randomization. Safety was assessed in the as-treated population, which included all the patients who received at least one dose of pembrolizumab or placebo. Patient-reported outcomes were analyzed in the population of all the patients who had undergone randomization, received at least one dose of pembrolizumab or placebo, and completed at least one patient-reported outcome assessment for the specific end point. Patient-reported outcomes were assessed with the use of the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS), which consists of nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fevers, and hematuria (the summary score ranges from 0 [all the worst symptoms] to 36 [no symptoms]; clinically meaningful change, ≥3 points); and the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30), on which scores range from 0 to 100, with higher scores indicating a higher level of quality of life or functioning (clinically meaningful change, ≥10 points). Detailed assessment schedules and methods are provided in the Supplementary Appendix.

TRIAL OVERSIGHT

The trial was designed by academic advisors and employees of the sponsor (Merck Sharp and Dohme, a subsidiary of Merck). The trial protocol and all the amendments were approved by the appropriate ethics body at each trial center. All the patients provided written informed consent before enrollment. The trial was conducted in accordance with Good Clinical Practice guidelines. An independent, external data and safety monitoring committee oversaw the trial and assessed efficacy and safety at the time of the prespecified interim analysis.

All the authors vouch for the accuracy and completeness of the data and attest that they had full access to all data in the trial and that they participated in writing or reviewing and editing drafts of the manuscript. The authors vouch for the fidelity of the trial to the protocol. As part of the site agreement, investigators agreed to keep all aspects of the trial, including the data, confidential. The sponsor participated in the trial design; the collection, analysis, and interpretation of the data; and the writing of the manuscript. The first draft of the manuscript was written by the first and last authors, with assistance from a medical writer employed by the sponsor.

STATISTICAL ANALYSIS

Disease-free survival and overall survival, as well as the respective percentages of patients who were alive and recurrence-free or alive at key time points, were estimated by means of the nonparametric Kaplan–Meier method. Hazard

ratios and 95% confidence intervals were estimated with the use of 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 that were used for randomization were applied to both the log-rank test and the Cox model.

We estimated that the enrollment of approximately 990 patients, with an expected 332 events of recurrence or death and an assumed proportion of cured patients of 0.3 from a Poisson mixture cure-rate model, would provide the trial with 95% power to detect a hazard ratio of 0.67 for pembrolizumab as compared with placebo at an alpha level of 2.5% (one-sided) in the primary analysis of disease-free survival. The overall type I error rate was strongly controlled at 2.5% with the use of a graphical method,[29] in which disease-free survival was tested first at an alpha level of 2.5%, and the alpha was passed to the analysis of overall survival if the null hypothesis of disease-free survival was rejected. A prespecified interim analysis was planned when approximately 265 events of recurrence or death, according to the investigator's assessment, had occurred and a minimum follow-up (defined as time that the last patient underwent randomization to the first interim analysis) of 12 months was reached. For the interim analysis reported here, the P-value boundary for significance was 0.0114 (one-sided) for the analysis of disease-free survival. The protocol specified the reporting of one-sided P values, but in accordance with *Journal* policy, two-sided P values are reported. According to the statistical analysis plan, approximately 200 deaths would be needed for the final analysis. A constrained longitudinal data analysis model[30] was applied to assess the mean change from baseline in patient-reported outcomes. Line plots for the empirical mean change from baseline over time were provided as a supportive analysis.

We used SAS software, version 9.4 (SAS), for all the statistical analyses. The full statistical analysis plan is provided in section 10 in the protocol.

RESULTS

PATIENTS AND TRIAL REGIMENS

Between June 30, 2017, and September 20, 2019, a total of 1406 patients at 213 sites in 21 countries underwent screening for trial eligibility (Fig. S1 in the Supplementary Appendix). Among the 412 excluded patients, the most common reasons for screening failure were the presence of baseline disease according to the investigator's assessment (in 37.9% of the excluded patients), not meeting the protocol-defined criteria for intermediate-to-high or high risk or M1 NED (in 16.0%), and withdrawal of consent during screening (in 15.8%). A total of 994 patients were randomly assigned to receive either adjuvant pembrolizumab (496 patients) or placebo (498 patients) (intention-to-treat population). A total of 488 patients received at least one dose of pembrolizumab, and 496 received at least one dose of placebo (as-treated population). As of the data-cutoff date of December 14, 2020, the median time from randomization to the data-cutoff date was 24.1 months (range, 14.9 to 41.5).

In the pembrolizumab group, 61.1% of the patients completed the full 17 cycles of trial treatment; 38.9% of the patients discontinued the trial regimen, with the most common reason being an adverse event (in 21.3%), followed by disease recurrence (in 10.5%). In the placebo group, 73.6% of the patients completed the full 17 cycles; 26.2% of the patients discontinued the trial regimen, with the most common reason being disease recurrence (in 20.4%). As of December 14, 2020, no patients were continuing to receive pembrolizumab or placebo, although one patient (0.2%) in the placebo group was not entered as such into the database until after the database lock. Therefore, no patients were continuing to receive pembrolizumab or placebo at the data-cutoff date.

The median duration of the trial regimen was 11.1 months (range, 0.0 to 14.3) in the pembrolizumab group and 11.1 months (range, 0.0 to 15.4) in the placebo group. Extensions of the treatment period beyond 12 months were due to delays in completing the 17 cycles as defined in the protocol. The median number of doses received was 17 (range, 1 to 17) in each group (Table S3). The 104 patients who discontinued pembrolizumab owing to an adverse event received a median of 7 cycles (range, 1 to 16), with a median exposure to pembrolizumab of 4.4 months (range, 0.03 to 11.1). Subsequent therapies are described in the Results section in the Supplementary Appendix.

The characteristics of the patients at baseline were generally similar in the two groups (Table 1

and S1). Most patients in the pembrolizumab group (86.1%) and in the placebo group (86.9%) had renal-cell carcinoma with M0 intermediate-to-high risk. In addition, 5.8% of the patients in each group had M1 NED status.

EFFICACY

As of the data-cutoff date, 260 events of disease recurrence or death had occurred (109 events in the pembrolizumab group and 151 in the placebo group). The median disease-free survival was not reached in either group (Fig. 1). The risk of disease recurrence or death was 32% lower with adjuvant pembrolizumab therapy than with placebo (hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P=0.002 [two-sided]). The estimated percentage of patients who remained alive and recurrence-free at 24 months was 77.3% (95% CI, 72.8 to 81.1) in the pembrolizumab group and 68.1% (95% CI, 63.5 to 72.2) in the placebo group; the corresponding percentages at 12 months were 85.7% (95% CI, 82.2 to 88.5) and 76.2% (95% CI, 72.2 to 79.7).

Local recurrence only was observed in 17 patients (3.4%) in the pembrolizumab group and in 32 (6.4%) in the placebo group. Distant recurrence was reported in 86 patients (17.3%) and 117 patients (23.5%), respectively. A prespecified sensitivity analysis of disease-free survival, which involved censoring at the last disease assessment before the start of a new anticancer therapy or because at least two consecutive assessments were missed if recurrence or death was documented immediately after the missed disease assessments, is shown in Figure S2. Disease-free survival across key subgroups is shown in Figure 1B.

A total of 51 deaths occurred (18 in the pembrolizumab group and 33 in the placebo group). The median overall survival was not reached in either group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96) (Fig. 2). The estimated percentage of patients who were alive at 24 months was 96.6% (95% CI, 94.3 to 98.0) in the pembrolizumab group and 93.5% (95% CI, 90.5 to 95.6) in the placebo group; the corresponding percentages at 12 months were 98.6% (95% CI, 97.0 to 99.3) and 98.0% (95% CI, 96.3 to 98.9).

SAFETY

In the as-treated population, 96.3% of the patients who received pembrolizumab and 91.1% of those who received placebo had at least one adverse event of any grade and of any cause

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab (N=496)	Placebo (N=498)
Age		
Median (range) — yr	60.0 (27–81)	60.0 (25–84)
≥65 yr — no. (%)	158 (31.9)	172 (34.5)
Male sex — no. (%)	347 (70.0)	359 (72.1)
ECOG performance-status score of 1 — no. (%)†	75 (15.1)	72 (14.5)
Geographic location		
North America	133 (26.8)	125 (25.1)
European Union‡	188 (37.9)	187 (37.6)
Rest of the world	175 (35.3)	186 (37.3)
Radical nephrectomy — no. (%)	459 (92.5)	460 (92.4)
Sarcomatoid features — no. (%)		
Present	52 (10.5)	59 (11.8)
Absent	417 (84.1)	415 (83.3)
Unknown	27 (5.4)	24 (4.8)
Disease risk category — no. (%)§		
M0, intermediate-to-high risk	427 (86.1)	433 (86.9)
M0, high risk	40 (8.1)	36 (7.2)
M1 NED¶	29 (5.8)	29 (5.8)
PD-L1 combined positive score — no. (%)‖		
<1	124 (25.0)	113 (22.7)
≥1	365 (73.6)	383 (76.9)
Missing data	7 (1.4)	2 (0.4)

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding.

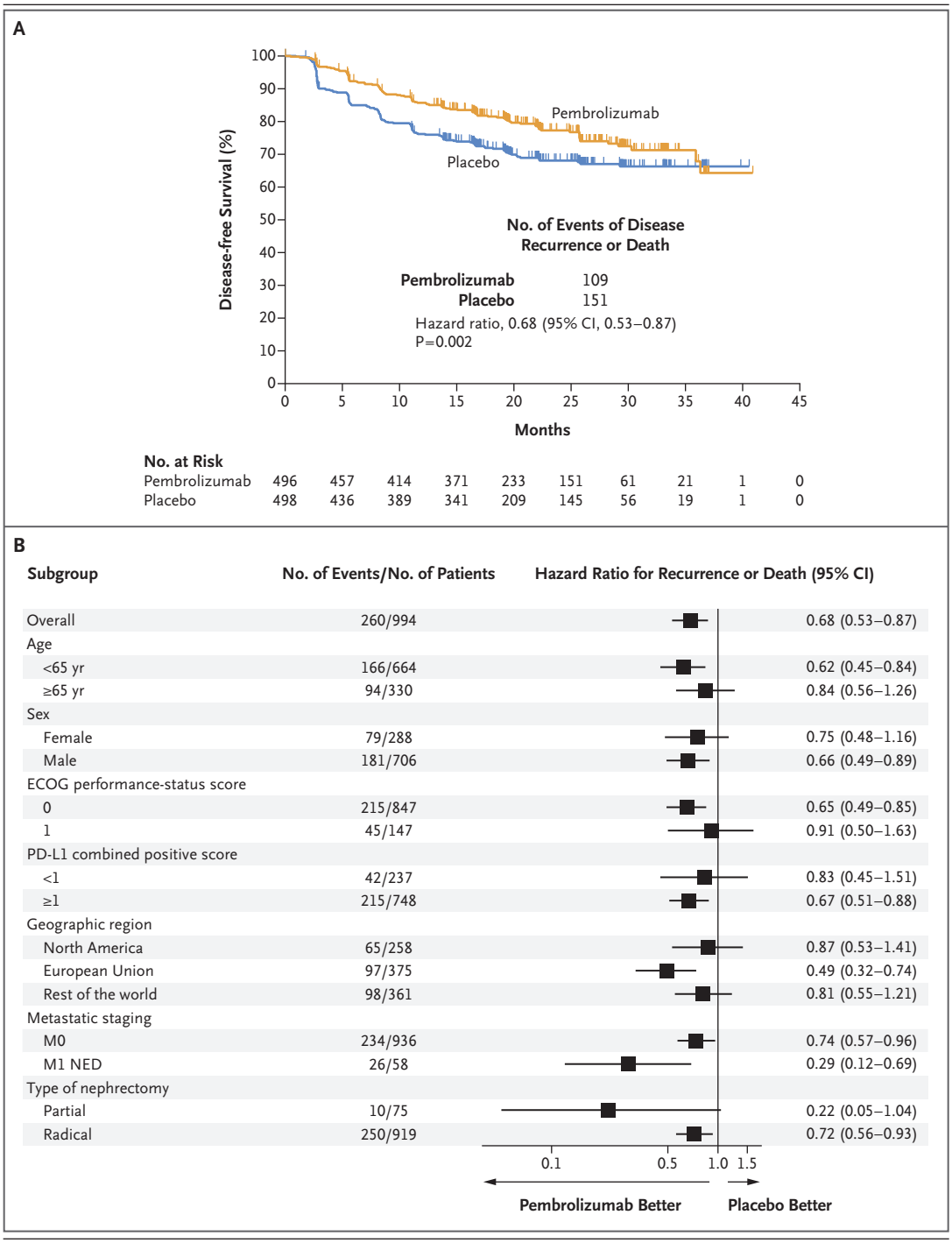
† Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a scale from 0 to 5, with higher scores indicating greater disability. A score of 1 indicates that strenuous physical activity is restricted but that the patient is fully ambulatory and able to carry out light work.

‡ The European Union included the United Kingdom at the time of the trial.

§ Patients with M0 (no metastases) disease and an intermediate-to-high risk of recurrence had disease staged as pT2 (grade 4 tumor or sarcomatoid), N0 (no nodal involvement), M0 or as pT3 (any grade), N0, M0. Patients with M0 disease and a high risk of recurrence had disease staged as pT4 (any grade of tumor), N0, M0 or as any pT (any grade of tumor), N+ (involvement of nearby nodes), M0. Patients who had disease categorized as M1 (metastasis in distant organ or tissue) NED (no evidence of disease) presented not only with the primary kidney tumor but also with solid, isolated, soft-tissue metastases that were completely resected at the time of nephrectomy (synchronous) or at 1 year or less after nephrectomy (metachronous). Five patients in the M0 intermediate-to-high risk group had T2 (grade ≤3 tumor), N0, M0 disease or T1 (tumor in kidney only of ≤7 cm in the greatest dimension), N0, M0 disease; these were protocol violations.

¶ Sites of metastasis in the subgroup of patients with M1 NED status at baseline are listed in Table S2.

‖ The programmed death ligand 1 (PD-L1) combined positive score was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.



(Table 2). In total, 32.4% of the patients who received pembrolizumab and 17.7% of those who received placebo had an adverse event of grade 3 to 5. There were two deaths in the pembrolizumab group, which were due to multiple organ dysfunction syndrome and pneumonia (in one patient each), and one death in the placebo group, which was due to intracranial hemorrhage. In addition, 20.5% of the patients who received pembrolizumab and 11.3% of those who received placebo had at least one serious adverse event (Table S5).

Figure 1 (facing page). Disease-free Survival (Intention-to-Treat Population).

Panel A shows the nonparametric Kaplan–Meier estimates of disease-free survival according to the investigator's assessment. The reported P value is two-sided. Tick marks represent data censored at the last time that the patient was known to be free from disease recurrence (i.e., at the time of the last imaging assessment). Panel B shows the analysis of disease-free survival according to key subgroups. The Eastern Cooperative Oncology Group (ECOG) performance-status score is assessed on a scale from 0 to 5, with higher scores indicating greater disability; a score of 0 indicates no restrictions on activity, and a score of 1 that strenuous physical activity is restricted but that the patient is fully ambulatory and able to carry out light work. The programmed death ligand 1 (PD-L1) combined positive score was defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100. The European Union included the United Kingdom at the time of the trial. Metastatic staging was categorized as M0 (absence of metastases) or M1 NED (no evidence of disease after resection of the primary tumor and solid, isolated, soft-tissue metastases). CI denotes confidence interval.

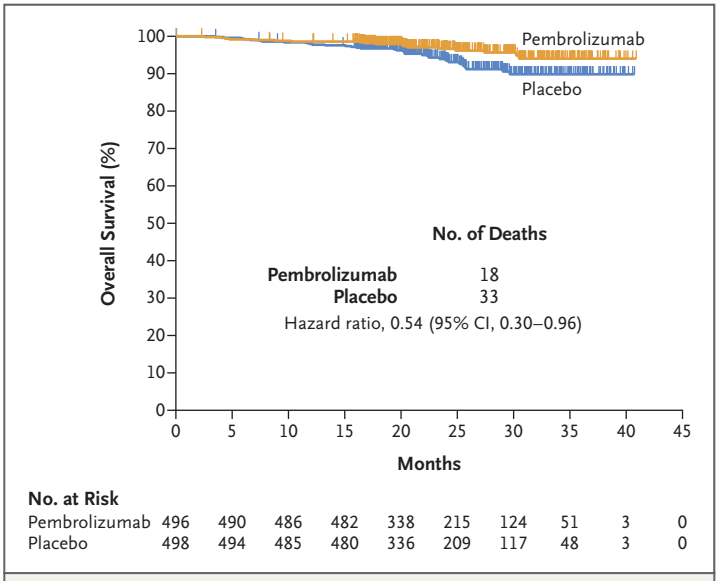


Figure 2. Overall Survival (Intention-to-Treat Population).

Shown are the Kaplan–Meier estimates of overall survival. Tick marks represent data censored at the last time the patient was known to be alive.

The most common adverse events of any cause in the two groups were fatigue (in 29.7% of the patients who received pembrolizumab and in 24.2% of those who received placebo), diarrhea (in 25.4% and 22.4%, respectively), pruritus (in 22.7% and 13.1%), and arthralgia (in 22.1% and 18.8%) (Table 3). The adverse events with the greatest risk difference between the pembrolizumab group and the placebo group were hypothyroidism, hyperthyroidism, pruritus, and rash (Fig. S3). In the as-treated population, 20.7% of the patients in the pembrolizumab group and 2.0% of those in the placebo group discontinued the respective trial regimen because of adverse events, the majority of which were nonserious (Table 2). Adverse events of any grade that led to the discontinuation of pembrolizumab or placebo are listed in Table S4. Among the patients who received pembrolizumab, only an increase in the alanine aminotransferase level (in 1.6%), adrenal insufficiency (in 1.0%), and colitis (in 1.0%) led to treatment discontinuation in 1.0% or more of the patients. Dose interruptions due to an adverse event were reported in 25.8% of the patients in the pembrolizumab group and in 14.9% of those in the placebo group.

A total of 386 patients (79.1%) who received pembrolizumab and 265 (53.4%) who received placebo had at least one adverse event of any grade that was attributed to pembrolizumab or placebo by the investigator, including an event of grade 3 or 4 in 18.9% of the patients who received pembrolizumab and 1.2% of those who received placebo. Treatment-related adverse events with an incidence of at least 5% in either group are listed in Table S6. No deaths that were attributed to either pembrolizumab or placebo occurred. At least one treatment-related serious adverse event occurred in 12.1% of the patients who received pembrolizumab and in 0.2% of those who received placebo.

Immune-mediated adverse events of any grade, according to a list of terms prespecified by the sponsor and considered regardless of attribution to pembrolizumab or placebo by the investigator, occurred in 34.6% of the patients who received pembrolizumab and in 5.8% of those who received placebo. Immune-mediated adverse events of grade 3 or 4 occurred in 8.6% of the patients who received pembrolizumab and in 0.6% of those who received placebo (Table S7). No deaths due to an immune-mediated adverse event occurred. During the treatment phase or the post-treatment phase of the trial, glucocorticoid use was recorded from the time of random-

Table 2. Any-Cause and Treatment-Related Adverse Events (As-Treated Population).*

Event	Pembrolizumab (N = 488)	Placebo (N = 496)
	no. of patients with event (%)	
Any-cause adverse events		
Adverse event of any grade	470 (96.3)	452 (91.1)
Adverse event of grade 3 to 5	158 (32.4)	88 (17.7)
Discontinuation of pembrolizumab or placebo due to adverse event	101 (20.7)	10 (2.0)
Death due to adverse event	2 (0.4)	1 (0.2)
Serious adverse event	100 (20.5)	56 (11.3)
Discontinuation of pembrolizumab or placebo due to serious adverse event	49 (10.0)	5 (1.0)
Treatment-related adverse events, as assessed by investigator		
Adverse event of any grade	386 (79.1)	265 (53.4)
Adverse event of grade 3 to 5	92 (18.9)	6 (1.2)
Discontinuation of pembrolizumab or placebo due to adverse event	86 (17.6)	3 (0.6)
Death due to adverse event	0	0
Serious adverse event	59 (12.1)	1 (0.2)
Discontinuation of pembrolizumab or placebo due to serious adverse event	37 (7.6)	0

* The as-treated population included all the patients who received at least one dose of pembrolizumab or placebo. Adverse events were recorded from randomization through 30 days after the discontinuation of pembrolizumab or placebo. Serious adverse events were defined as any adverse event that resulted in death, was life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was judged by the investigator to be a serious adverse event. Serious adverse events were recorded from randomization through 90 days after the discontinuation of pembrolizumab or placebo.

ization to the data-cutoff date or death, whichever occurred first. A total of 7.4% of the patients who received pembrolizumab and 0.6% of those who received placebo received high-dose systemic glucocorticoid treatment (≥40 mg per day) for immune-mediated adverse events.

PATIENT-REPORTED OUTCOMES

The full analysis population for patient-reported outcomes included 483 patients in the pembrolizumab group and 493 patients in the placebo group for the FKSI-DRS tool and 484 and 493 patients, respectively, for the EORTC QLQ-C30 tool. At baseline in the pembrolizumab group, 435 patients (90.1%) completed the FKSI-DRS assessment and 438 patients (90.5%) completed the EORTC QLQ-C30 assessment; the corresponding values in the placebo group were 447 patients (90.7%) and 450 patients (91.3%). At 52 weeks into the treatment phase, in the pembrolizumab group, 300 patients (62.1%) completed the FKSI-DRS assessment and 301 patients (62.2%) completed the EORTC QLQ-C30 assessment; the corresponding values in the placebo group were 328 patients (66.5%) and 325 patients (65.9%).

The least-squares mean change from baseline to week 52 in the FKSI-DRS score was −1.12 (95% CI, −1.53 to −0.71) in the pembrolizumab group and −0.45 (95% CI, −0.84 to −0.05) in the placebo group. The least-squares mean change from baseline to week 52 in the EORTC QLQ-C30 physical functioning score was −1.81 (95% CI, −3.19 to −0.43) in the pembrolizumab group and −0.90 (95% CI, −2.23 to 0.44) in the placebo group. The empirical mean changes over time in the FKSI-DRS score and the EORTC QLQ-C30 physical functioning score are provided in Figure S4.

Table 3. Any-Cause Adverse Events with an Incidence of at Least 10% in Either Group (As-Treated Population).*

Event	Pembrolizumab (N=488)		Placebo (N=496)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
Fatigue	145 (29.7)	5 (1.0)	120 (24.2)	0
Diarrhea	124 (25.4)	8 (1.6)	111 (22.4)	1 (0.2)
Pruritus	111 (22.7)	1 (0.2)	65 (13.1)	0
Arthralgia	108 (22.1)	2 (0.4)	93 (18.8)	2 (0.4)
Hypothyroidism	103 (21.1)	1 (0.2)	18 (3.6)	0
Rash	98 (20.1)	4 (0.8)	53 (10.7)	2 (0.4)
Nausea	80 (16.4)	2 (0.4)	48 (9.7)	0
Cough	76 (15.6)	0	50 (10.1)	0
Headache	69 (14.1)	0	62 (12.5)	0
Hyperthyroidism	58 (11.9)	1 (0.2)	1 (0.2)	0
Asthenia	50 (10.2)	1 (0.2)	36 (7.3)	1 (0.2)
Increase in blood creatinine level	50 (10.2)	1 (0.2)	42 (8.5)	0
Back pain	49 (10.0)	1 (0.2)	64 (12.9)	1 (0.2)

* No adverse events of grade 4 or 5 occurred in at least 10% of the patients in either group.

DISCUSSION

At the prespecified first interim analysis, the randomized, phase 3 KEYNOTE-564 trial showed that adjuvant pembrolizumab therapy conferred a significant and clinically meaningful improvement in disease-free survival (primary end point), as compared with placebo, among patients with renal-cell carcinoma who were at intermediate-to-high risk or high risk for recurrence after nephrectomy or who had M1 NED status after nephrectomy and resection of metastatic lesions. Investigator assessment was selected for the primary end point because investigators are able to assess the presence or absence of disease in real time, and this design is generally in line with clinical practice. The disease-free survival curves separated early and remained separated, with a steady difference in the estimated disease-free survival of at least 9 percentage points at 12 months and 24 months. The numbers at risk beyond the median follow-up of 24 months were small. Thus, the Kaplan–Meier estimates in the tails of the curves were based on censored data, were not stable, and should be interpreted with caution. The benefit with regard to disease-free survival was generally consistent across subgroups, although the numbers of patients and events were small in some subgroups and therefore should be interpreted with caution. Of note, a subgroup of patients (5.8%) with resected advanced disease (M1 NED) was included in the trial. The observed benefit of pembrolizumab as compared with placebo was maintained in this population, although the numbers of patients were small and precluded definitive interpretation. The overall survival analysis was immature at the data-cutoff date and included only 26% of the total deaths that were expected as prespecified for the final analysis.

No new safety signals with pembrolizumab therapy were observed. No treatment-related deaths occurred in patients who received pembrolizumab. As expected, the incidences of grade 3 to 5 adverse events of any cause, of serious adverse events, and of treatment-related adverse events of any grade or of grade 3 or 4 were higher in the pembrolizumab group than in the placebo group. Adverse events with the greatest risk difference between the pembrolizumab group and the placebo group, such as hyperthyroidism, hypothyroidism, and pruritus, were all known

and expected with pembrolizumab monotherapy[24,31-35] and were manageable. The frequencies of individual grade 3 or 4 immune-mediated adverse events remained around or lower than 1% and were in line with expectations. Safety results in the placebo group were in line with expectations that were based on previous reports.[10,34]

The threshold for clinically meaningful change in the FKSI-DRS score is a change of at least 3 and in the EORTC QLQ-C30 score is a change of at least 10.[36-38] No clinically meaningful changes from the baseline scores in either instrument were observed with adjuvant pembrolizumab therapy or placebo. Findings regarding patient-reported outcomes suggested that health-related quality-of-life and symptom scores were stable in the pembrolizumab group over the entire trial period and that there were no meaningful differences in scores as compared with the placebo group. These results suggested that the adverse-event profile of adjuvant pembrolizumab therapy was acceptable from a patient's perspective.

A limitation of the current analysis was the extended enrollment of patients in the trial, which resulted in a large amount of data censoring beyond 2 years of follow-up. Given that this analysis was the first prespecified analysis of the trial, longer follow-up is needed to determine proportions of definitively cured patients and the effect on overall survival.

The growing global incidence of localized renal-cell carcinoma, paired with the persistent probability of disease recurrence after surgery, places emphasis on the usefulness of an effective adjuvant treatment strategy for patients with this tumor type.[3,39] VEGF-targeted therapies and other approaches have not shown a consistent benefit in patients with such disease.[1,2,39,40] The results of this phase 3 trial support the use of pembrolizumab as adjuvant immunotherapy in patients with renal-cell carcinoma and an intermediate-to-high or high risk of disease recurrence.

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APPENDIX

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