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# Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma

T.K. Choueiri, P. Tomczak, S.H. Park, B. Venugopal, T. Ferguson, S.N. Symeonides, J. Hajek, Y.-H. Chang, J.-L. Lee, N. Sarwar, N.B. Haas, H. Gurney, P. Sawrycki, M. Mahave, M. Gross-Goupil, T. Zhang, J.M. Burke, G. Doshi, B. Melichar, E. Kopyltsov, A. Alva, S. Oudard, D. Topart, H. Hammers, H. Kitamura, D.F. McDermott, A. Silva, E. Winquist, J. Cornell, A. Elfiky, J.E. Burgents, R.F. Perini, and T. Powles, for the KEYNOTE-564 Investigators*

## ABSTRACT

### BACKGROUND

Adjuvant pembrolizumab therapy after surgery for renal-cell carcinoma was approved on the basis of a significant improvement in disease-free survival in the KEYNOTE-564 trial. Whether the results regarding overall survival from the third prespecified interim analysis of the trial would also favor pembrolizumab was uncertain.

### METHODS

In this phase 3, double-blind, placebo-controlled trial, we randomly assigned (in a 1:1 ratio) participants with clear-cell renal-cell carcinoma who had an increased risk of recurrence after surgery to receive pembrolizumab (at a dose of 200 mg) or placebo every 3 weeks for up to 17 cycles (approximately 1 year) or until recurrence, the occurrence of unacceptable toxic effects, or withdrawal of consent. A significant improvement in disease-free survival according to investigator assessment (the primary end point) was shown previously. Overall survival was the key secondary end point. Safety was a secondary end point.

### RESULTS

A total of 496 participants were assigned to receive pembrolizumab and 498 to receive placebo. As of September 15, 2023, the median follow-up was 57.2 months. The disease-free survival benefit was consistent with that in previous analyses (hazard ratio for recurrence or death, 0.72; 95% confidence interval [CI], 0.59 to 0.87). A significant improvement in overall survival was observed with pembrolizumab as compared with placebo (hazard ratio for death, 0.62; 95% CI, 0.44 to 0.87; P=0.005). The estimated overall survival at 48 months was 91.2% in the pembrolizumab group, as compared with 86.0% in the placebo group; the benefit was consistent across key subgroups. Pembrolizumab was associated with a higher incidence of serious adverse events of any cause (20.7%, vs. 11.5% with placebo) and of grade 3 or 4 adverse events related to pembrolizumab or placebo (18.6% vs. 1.2%). No deaths were attributed to pembrolizumab therapy.

### CONCLUSIONS

Adjuvant pembrolizumab was associated with a significant and clinically meaningful improvement in overall survival, as compared with placebo, among participants with clear-cell renal-cell carcinoma at increased risk for recurrence after surgery. (Funded by Merck Sharp and Dohme, a subsidiary of Merck; KEYNOTE-564 ClinicalTrials.gov number, NCT03142334.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Choueiri can be contacted at toni_choueiri@dfci.harvard.edu or at Dana–Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215.

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

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CME

A Quick Take is available at NEJM.org

Adjuvant therapy after surgery for localized renal-cell carcinoma has historically been a challenging area of investigation with limited success. Among the multiple vascular endothelial growth factor (VEGF) receptor–tyrosine kinase inhibitors (VEGFR-TKIs) that have been tested in this context, only sunitinib showed an efficacy benefit and in only one of two randomized trials.[1-6] Furthermore, although the phase 3 Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy (S-TRAC) trial showed a significant improvement in disease-free survival (the primary end point) with adjuvant sunitinib as compared with placebo, whereas the larger phase 3, placebo-controlled Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial of sunitinib did not, no prolongation in overall survival has been reported with an adjuvant VEGFR-TKI.[1,6,7] Until 2021, sunitinib was the only therapy that had been approved in the United States for adjuvant use in adult patients at high risk for recurrent renal-cell carcinoma after nephrectomy, and no treatments that were supported by high levels of evidence were used worldwide.

Pembrolizumab, an anti–programmed death 1 (PD-1) antibody, was approved in 2021 as adjuvant treatment for patients with renal-cell carcinoma who were at an intermediate-to-high or high risk for recurrence after nephrectomy, with or without the resection of metastatic lesions.[8] This approval was based on the significant and clinically meaningful improvement in disease-free survival that was observed with pembrolizumab in the phase 3, double-blind, randomized, placebo-controlled KEYNOTE-564 trial (estimated 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).[9] Other treatment approaches with adjuvant immune checkpoint inhibition after surgery in renal-cell carcinoma have also been investigated, including monotherapy with an anti–programmed death ligand 1 (PD-L1) antibody (atezolizumab) for up to 1 year in the phase 3 IMmotion010 trial and the combination of anti–PD-1 and anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies (nivolumab plus ipilimumab) for up to 6 months in the phase 3 CheckMate 914 trial.[10,11] Neither of these trials showed a difference in disease-free survival.

Data for the key secondary end point of overall survival in the KEYNOTE-564 trial were not sufficiently mature at the time of the previous interim analyses.[9,12] We present here the results of the third prespecified interim analysis of this trial.

## METHODS

### TRIAL DESIGN AND INTERVENTIONS

We conducted a phase 3, double-blind, randomized, placebo-controlled trial involving patients who were disease-free on the basis of investigator assessment after surgery for clear-cell renal-cell carcinoma. Participants were randomly assigned (in a 1:1 ratio) to receive intravenous pembrolizumab (at a dose of 200 mg) or matched placebo every 3 weeks for up to 17 cycles (approximately 1 year) or until disease recurrence, the occurrence of unacceptable toxic effects, or a decision to discontinue pembrolizumab or placebo by the participant or physician. Detailed methods have been published previously[9,12] and are provided in the trial protocol, which is available with the full text of this article at NEJM.org.

Randomization was stratified according to metastatic stage before surgery (M0 [no metastases] vs. M1 [metastasis in a distant organ or tissue]). Within the M0 subgroup, randomization was further stratified according to the Eastern Cooperative Oncology Group (ECOG) performance-status score (0 vs. 1; scores range from 0 to 5, with higher scores indicating greater disability) and geographic region (United States vs. other). Prespecified interim analyses were built into the trial to allow for an independent, external data and safety monitoring committee to monitor the safety and efficacy of the investigational treatment throughout the trial and to make recommendations regarding the overall risk and benefit to the participants.

### PARTICIPANTS

Eligible participants were adults with confirmed clear-cell renal-cell carcinoma who had undergone surgery within 12 weeks before randomization. Surgery could include partial or radical nephrectomy and synchronous or metachronous (within 1 year after nephrectomy) metastasectomy of any solid, isolated, soft-tissue, nonosseous, nonbrain metastatic lesions that could be resected completely with negative surgical margins.

The risk of disease recurrence was classified according to protocol-defined criteria as intermediate to high (tumor stage T2 with nuclear grade 4 or sarcomatoid features, or tumor stage T3; no regional lymph node or distant metastasis present), high (tumor stage T4 with no regional lymph node or distant metastasis, or any tumor stage with the presence of regional lymph-node involvement), or stage M1 NED (no evidence of disease).

### END POINTS AND ASSESSMENTS

Disease-free survival according to the investigator's assessment (defined as the time from randomization to the first documented recurrence of renal-cell carcinoma or death from any cause, whichever occurred first) was the primary end point. Overall survival (defined as the time from randomization to death from any cause) was the key secondary end point. Secondary end points included safety and participant-reported outcomes as assessed with the use of the Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) questionnaire and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30).

Follow-up assessments for survival status and the initiation of subsequent anticancer therapy occurred every 12 weeks. Participants without an event (recurrence or death) had their data censored for disease-free survival at the last measurement and for overall survival at the last contact. Subsequent therapies were administered at the discretion of the investigator with no restrictions. Unblinding of the trial-group assignments to the investigator in order to support subsequent treatment decisions was permitted. Serious adverse events that were attributed by the investigator to pembrolizumab or placebo were reported regardless of when they occurred, including during follow-up (>90 days after the discontinuation of pembrolizumab or placebo) up to the data-cutoff date or participant withdrawal of consent. The FKSI-DRS and EORTC QLQ-C30 were administered electronically at cycles 1, 5, 9, 13, and 17; at the discontinuation of pembrolizumab or placebo; at 30 days after the receipt of the last dose; and annually thereafter until recurrence, the receipt of new anticancer therapy, or withdrawal of consent.

### TRIAL OVERSIGHT

The appropriate ethics body at each treatment center approved the trial protocol and all amendments. The trial was conducted in accordance with Good Clinical Practice guidelines and was overseen by an independent, external data and safety monitoring committee that evaluated efficacy and safety at prespecified interim analyses. Written informed consent was obtained from all the participants. As part of the site agreement, investigators agreed to keep all aspects of the trial, including the data, confidential. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All the authors attest that they had full access to all the data in the trial, participated in writing or reviewing and editing the manuscript, and approved the decision to submit the manuscript for publication. The sponsor (Merck Sharp and Dohme, a subsidiary of Merck) participated in the trial design; the collection, analysis, and interpretation of the data; and the writing of the manuscript. A medical writer who was employed by the sponsor assisted with manuscript preparation.

### STATISTICAL ANALYSIS

At the first interim analysis, disease-free survival (the primary end point) was significantly improved with pembrolizumab as compared with placebo; this end point was not formally tested again, in accordance with the statistical analysis plan.[9] The overall type I error was controlled at 5.0% (two-sided) with the use of the graphical method of Maurer and Bretz.[13] Once the null hypothesis for disease-free survival was rejected, the alpha of 0.05 was passed to overall survival. For an approximate sample of 990 enrolled participants, the third interim analysis was planned to take place after approximately 132 deaths had occurred; according to the statistical analysis plan, 200 deaths would be needed for the final analysis. The trial had 79% power to detect a hazard ratio for death of 0.67 or had 88% power to detect a hazard ratio for death of 0.635. A Lan–DeMets O'Brien–Fleming alpha-spending function was used to set efficacy boundaries.

For the present analysis, the P-value boundary for significant improvement in overall survival was 0.0144 (two-sided). The protocol specified the reporting of one-sided P values, but in accordance

with *Journal* policy, two-sided P values are reported here. Therefore, the two-sided overall alpha level and two-sided P-value boundary for overall survival are provided. The full statistical analysis plan is available with the trial protocol. If the null hypothesis for overall survival were to be rejected in the current analysis, this would become the primary analysis for overall survival, and no further formal testing of this hypothesis would occur.

Efficacy end points were assessed in the intention-to-treat population, which included all the participants who underwent randomization. Safety was assessed in the as-treated population, which included all the participants who underwent randomization and received at least one dose of pembrolizumab or placebo. The nonparametric Kaplan–Meier method was used to estimate the median disease-free survival and overall survival and event rates at key time points. A stratified Cox proportional-hazards model with Efron's method of tie handling with trial group as a single covariate was used to estimate hazard ratios and 95% two-sided confidence intervals. A stratified log-rank test was used to test between-group differences in efficacy. SAS software, version 9.4 (SAS), was used for all the statistical analyses.

## RESULTS

### PARTICIPANTS AND TRIAL REGIMENS

As previously described,[9,12] 994 participants were randomly assigned to receive adjuvant pembrolizumab (496) or placebo (498). The median time from randomization to the data-cutoff date (September 15, 2023) was 57.2 months (range, 47.9 to 74.5). The demographic and disease characteristics of the participants at baseline and the reasons for the discontinuation of pembrolizumab or placebo were largely unchanged from previous reports (Table 1 and Table S1 and Fig. S1 in the Supplementary Appendix, available at NEJM.org).[9,12] The median duration of the trial regimen remained 11.1 months (range, 0.03 to 14.3) in the pembrolizumab group and 11.1 months (range, 0.03 to 15.4) in the placebo group. The median number of doses of pembrolizumab or placebo remained 17 (range, 1 to 17). All the participants had completed or discontinued the trial regimen by December 2020.

### EFFICACY

A total of 55 participants in the pembrolizumab group and 86 participants in the placebo group died. The overall rate of death was 0.2 deaths per 100 person-months in the pembrolizumab group and 0.3 deaths per 100 person-months in the placebo group. The estimated percentage of participants who were alive in the pembrolizumab group was 96.3% (95% CI, 94.2 to 97.7) at 24 months, 93.9% (95% CI, 91.4 to 95.7) at 36 months, and 91.2% (95% CI, 88.3 to 93.4) at 48 months. The estimated percentage of participants who were alive in the placebo group was 93.9% (95% CI, 91.4 to 95.7) at 24 months, 89.5% (95% CI, 86.4 to 91.9) at 36 months, and 86.0% (95% CI, 82.6 to 88.8) at 48 months. The risk of death was estimated to be 38% lower with pembrolizumab than with placebo, and a significant improvement in the key secondary end point of overall survival was observed (hazard ratio for death, 0.62; 95% CI, 0.44 to 0.87; P=0.005) (Fig. 1A).

These are updated results. The previous analyses of overall survival occurred after a median follow-up of 24.1 months (estimated percentage of participants who were alive at 24 months, 96.6% in the pembrolizumab group vs. 93.5% in the placebo group; hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96)[9] and after a median follow-up of 30.1 months (estimated percentage of participants who were alive at 24 months, 96.2% vs. 93.8%; hazard ratio for death, 0.52; 95% CI, 0.31 to 0.86).[12,14]

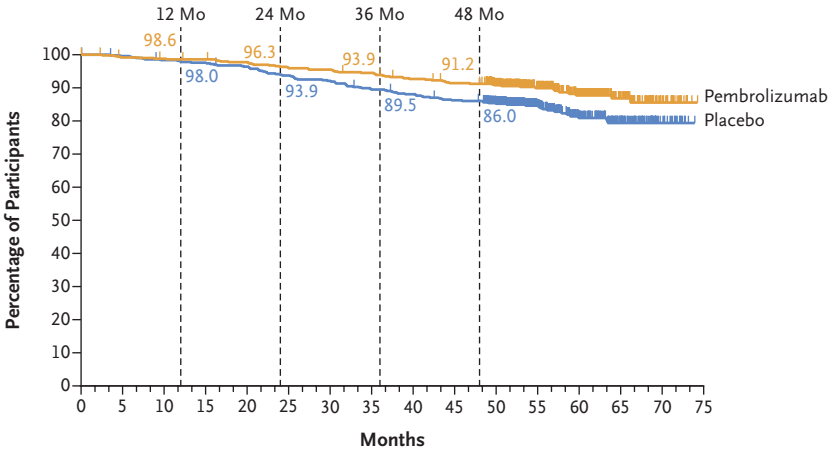
The overall survival benefit across key subgroups is shown in Figure 1B. Sample sizes and the numbers of deaths in some subgroups were small, and confidence intervals were wide. The overall survival benefit was also consistent in the protocol-prespecified subgroup of participants who had M0 stage disease and an intermediate-to-high risk of recurrence (survival at 48 months, 92.6% in the pembrolizumab group vs. 87.7% in the placebo group; hazard ratio for death, 0.59; 95% CI, 0.40 to 0.87). The number of deaths was small in the subgroup of participants who had M0 stage disease and a high risk of recurrence (19 deaths among 77 participants; survival at 48 months, 80.0% vs. 73.0%; hazard ratio for death, 0.78; 95% CI, 0.32 to 1.93) and in the subgroup of participants with M1 NED status (11 deaths among 57 participants; survival at 48 months,

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

| Characteristic | Pembrolizumab (N=496) | Placebo (N=498) |
|---|---|---|
| Age | | |
| Median (range) — yr | 60 (27–81) | 60 (25–84) |
| ≥65 yr — no. (%) | 158 (31.9) | 172 (34.5) |
| Male sex — no. (%) | 347 (70.0) | 359 (72.1) |
| Race or ethnic group — no. (%)† | | |
| American Indian or Alaska Native | 10 (2.0) | 2 (0.4) |
| Asian | 63 (12.7) | 75 (15.1) |
| Black | 7 (1.4) | 5 (1.0) |
| Multiple | 8 (1.6) | 5 (1.0) |
| White | 372 (75.0) | 376 (75.5) |
| Missing data | 36 (7.3) | 35 (7.0) |
| ECOG performance-status score of 1 — no. (%)‡ | 75 (15.1) | 72 (14.5) |
| 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) |
| Geographic location — no. (%) | | |
| North America | 133 (26.8) | 125 (25.1) |
| European Union | 188 (37.9) | 187 (37.6) |
| Rest of world | 175 (35.3) | 186 (37.3) |
| Geographic region — no. (%) | | |
| United States | 114 (23.0) | 117 (23.5) |
| Other | 382 (77.0) | 381 (76.5) |
| Radical nephrectomy — no. (%) | 459 (92.5) | 459 (92.2) |
| Disease risk category — no. (%)¶ | | |
| M0 intermediate-to-high risk | 422 (85.1) | 433 (86.9) |
| M0 high risk | 40 (8.1) | 37 (7.4) |
| M0 other | 5 (1.0) | 0 |
| M1 NED | 29 (5.8) | 28 (5.6) |
| Sarcomatoid features — no. (%) | | |
| Present | 52 (10.5) | 59 (11.8) |
| Absent | 414 (83.5) | 415 (83.3) |
| Unknown | 30 (6.0) | 24 (4.8) |

* The intention-to-treat population included all the participants who underwent randomization. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participant.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and 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 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.
¶ Participants with M0 (no metastases) disease and an intermediate-to-high risk of recurrence had disease staged as T2 (grade 4 tumor or sarcomatoid), N0 (no nodal involvement), M0 or as T3 (any grade), N0, M0. Participants with M0 disease and a high risk of recurrence had disease staged as T4 (any grade of tumor), N0, M0 or as any T (any grade of tumor), node-positive, M0. Participants 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 no more than 1 year after nephrectomy (metachronous). Participants in the "M0 other" subgroup had disease staged as T2 (grade ≤3 tumor) N0, M0 or as T1, N0, M0 disease (protocol violations).

**A Overall Survival in the Intention-to-Treat Population**




**No. at Risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 496 | 489 | 486 | 484 | 479 | 470 | 468 | 462 | 451 | 443 | 397 | 270 | 168 | 81 | 22 | 0 |
| Placebo | 498 | 494 | 487 | 483 | 476 | 463 | 455 | 441 | 433 | 423 | 382 | 248 | 155 | 79 | 22 | 0 |

**B Subgroup Analysis for Overall Survival**

| Subgroup | Pembrolizumab | Placebo | Hazard Ratio for Death (95% CI) |
|---|---|---|---|
| | *no. of deaths/no. of participants* | | |
| Overall | 55/496 | 86/498 | 0.62 (0.44–0.87) |
| Age | | | |
| <65 yr | 25/338 | 46/326 | 0.51 (0.31–0.83) |
| ≥65 yr | 30/158 | 40/172 | 0.77 (0.48–1.23) |
| Sex | | | |
| Female | 20/149 | 18/139 | 1.08 (0.57–2.04) |
| Male | 35/347 | 68/359 | 0.50 (0.33–0.75) |
| Race | | | |
| White | 46/372 | 67/376 | 0.67 (0.46–0.98) |
| Other | 6/88 | 13/87 | 0.45 (0.17–1.20) |
| ECOG performance-status score | | | |
| 0 | 38/421 | 67/426 | 0.55 (0.37–0.82) |
| 1 | 17/75 | 19/72 | 0.84 (0.44–1.63) |
| PD-L1 combined positive score | | | |
| <1 | 12/124 | 16/113 | 0.65 (0.31–1.38) |
| ≥1 | 42/365 | 69/383 | 0.62 (0.42–0.91) |
| Geographic region | | | |
| United States | 11/114 | 16/117 | 0.68 (0.32–1.47) |
| Other | 44/382 | 70/381 | 0.61 (0.42–0.88) |
| Metastatic staging | | | |
| M0 | 51/467 | 79/470 | 0.63 (0.44–0.90) |
| M1 NED | 4/29 | 7/28 | 0.51 (0.15–1.75) |
| Disease risk category | | | |
| M0 intermediate-to-high risk | 41/422 | 69/433 | 0.59 (0.40–0.87) |
| M0 high risk | 9/40 | 10/37 | 0.78 (0.32–1.93) |
| M1 NED | 4/29 | 7/28 | 0.51 (0.15–1.75) |
| Sarcomatoid features | | | |
| Present | 8/52 | 12/59 | 0.69 (0.28–1.70) |
| Absent | 41/414 | 70/415 | 0.57 (0.39–0.84) |

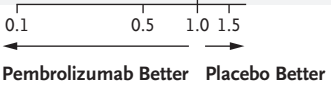


**Figure 1 (facing page). Overall Survival (Intention-to-Treat Population).**

Panel A shows nonparametric Kaplan–Meier estimates of overall survival in the intention-to-treat population at the third interim analysis. The intention-to-treat population included all the participants who had undergone randomization. Tick marks indicate data censored at the last time the participant was known to be alive. Panel B shows overall survival according to key subgroups. Hazard ratios and two-sided 95% confidence intervals were estimated with the use of a stratified Cox regression model for overall survival at the third interim analysis. Race was reported by the participant. Eastern Cooperative Oncology Group (ECOG) performance-status scores are 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. 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). Arrows indicate that the confidence interval extends outside the graphed area.

89.7% vs. 78.0%; hazard ratio for death, 0.51; 95% CI, 0.15 to 1.75) (Fig. S2).

Disease recurrence or death occurred in 174 participants (161 recurrences and 13 deaths without documented recurrence) in the pembrolizumab group and in 224 participants (210 recurrences and 14 deaths without documented recurrence) in the placebo group. The event rate in the analysis of disease-free survival was 0.9 events per 100 person-months in the pembrolizumab group and 1.2 events per 100 person-months in the placebo group. The estimated percentage of participants who were alive and free from recurrence in the pembrolizumab group was 78.2% (95% CI, 74.2 to 81.6) at 24 months, 72.4% (95% CI, 68.1 to 76.2) at 36 months, and 64.9% (95% CI, 60.3 to 69.1) at 48 months. The estimated percentage of participants who were alive and free from recurrence in the placebo group was 67.2% (95% CI, 62.8 to 71.1) at 24 months, 62.9% (95% CI, 58.5 to 67.0) at 36 months, and 56.6% (95% CI, 52.0 to 60.9) at 48 months. The hazard ratio for disease recurrence or death was 0.72 (95% CI, 0.59 to 0.87) (Fig. 2A).

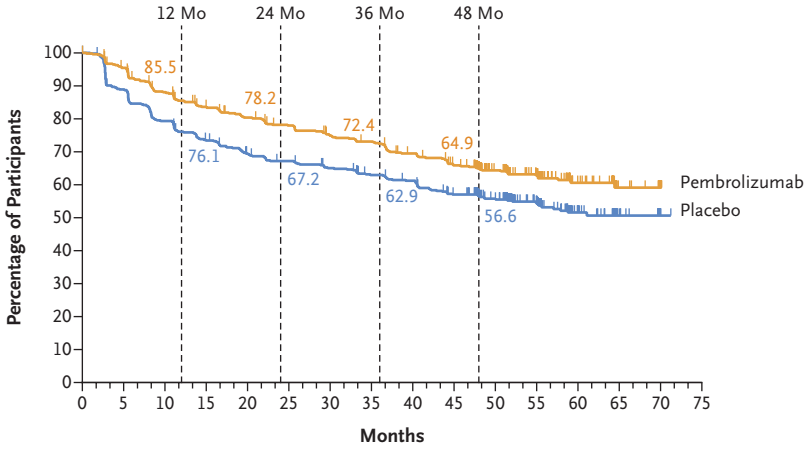
These are updated results. The previous analysis of disease-free survival occurred after a median follow-up of 24.1 months (estimated percentage of participants who were alive and free from recurrence at 24 months, 77.3% in the pembrolizumab group vs. 68.1% in the placebo group; hazard ratio for recurrence or death, 0.68; 95% CI, 0.53 to 0.87; P=0.002)[9] and after a median follow-up of 30.1 months (estimated percentage of participants who were alive and free from recurrence at 24 months, 78.3% vs. 67.3%; hazard ratio for recurrence or death, 0.63; 95% CI, 0.50 to 0.80).[12,14] The disease-free survival benefit was generally consistent across the analyzed subgroups (Fig. 2B).

### SUBSEQUENT THERAPY

Among the 161 participants with documented recurrence in the pembrolizumab group, 25 (15.5%) had local recurrence and 143 (88.8%) had distant recurrence. Among the 210 participants with documented recurrence in the placebo group, 43 (20.5%) had local recurrence and 179 (85.2%) had distant recurrence (Table S2).

Among participants with any documented recurrence, 128 of 161 (79.5%) in the pembrolizumab group and 171 of 210 (81.4%) in the placebo group were known to have received some form of subsequent therapy. An additional 4 participants in the pembrolizumab group and 1 participant in the placebo group received subsequent therapy, but recurrence was not documented. Among all the participants who received subsequent therapy, 79.5% (105 of 132) in the pembrolizumab group and 84.3% (145 of 172) in the placebo group received systemic anticancer drug therapy; 24.2% (32 of 132) and 19.8% (34 of 172), respectively, received radiation therapy; and 27.3% (36 of 132) and 29.1% (50 of 172) underwent further surgery (Table 2). Among the participants who received any systemic therapy, subsequent anti–PD-1 or anti–PD-L1 antibody-based therapy was received by 41.0% of the participants (43 of 105) in the pembrolizumab group and by 69.7% of those (101 of 145) in the placebo group. In addition, among the participants who received any systemic therapy, subsequent VEGF- or VEGFR-targeted therapy was

**A** Disease-free Survival in the Intention-to-Treat Population




**No. at Risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 496 | 458 | 416 | 388 | 370 | 355 | 337 | 327 | 307 | 284 | 221 | 160 | 65 | 19 | 5 | 0 |
| Placebo | 498 | 438 | 390 | 357 | 333 | 320 | 307 | 292 | 282 | 254 | 210 | 139 | 62 | 16 | 2 | 0 |

**B** Subgroup Analysis for Disease-free Survival

| Subgroup | Pembrolizumab | Placebo | Hazard Ratio for Recurrence or Death (95% CI) |
|---|---|---|---|
| | *no. of events/no. of participants* | | |
| Overall | 174/496 | 224/498 | 0.72 (0.59–0.87) |
| Age | | | |
| <65 yr | 117/338 | 135/326 | 0.77 (0.60–0.98) |
| ≥65 yr | 57/158 | 89/172 | 0.67 (0.48–0.93) |
| Sex | | | |
| Female | 50/149 | 63/139 | 0.68 (0.47–0.99) |
| Male | 124/347 | 161/359 | 0.74 (0.59–0.94) |
| Race | | | |
| White | 130/372 | 170/376 | 0.73 (0.58–0.91) |
| Other | 33/88 | 41/87 | 0.72 (0.45–1.13) |
| ECOG performance-status score | | | |
| 0 | 147/421 | 188/426 | 0.73 (0.59–0.90) |
| 1 | 27/75 | 36/72 | 0.71 (0.43–1.16) |
| PD-L1 combined positive score | | | |
| <1 | 37/124 | 36/113 | 0.91 (0.58–1.44) |
| ≥1 | 133/365 | 187/383 | 0.68 (0.55–0.85) |
| Geographic region | | | |
| United States | 38/114 | 55/117 | 0.69 (0.46–1.05) |
| Other | 136/382 | 169/381 | 0.74 (0.59–0.92) |
| Metastatic staging | | | |
| M0 | 161/467 | 203/470 | 0.75 (0.61–0.93) |
| M1 NED | 13/29 | 21/28 | 0.40 (0.20–0.81) |
| Disease risk category | | | |
| M0 intermediate-to-high risk | 138/422 | 177/433 | 0.76 (0.61–0.95) |
| M0 high risk | 22/40 | 26/37 | 0.61 (0.35–1.08) |
| M1 NED | 13/29 | 21/28 | 0.40 (0.20–0.81) |
| Sarcomatoid features | | | |
| Present | 22/52 | 33/59 | 0.63 (0.37–1.08) |
| Absent | 139/414 | 179/415 | 0.73 (0.59–0.91) |

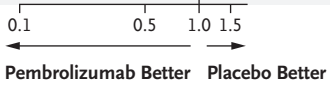


**Figure 2 (facing page). Disease-free Survival (Intention-to-Treat Population).**

Panel A shows the nonparametric Kaplan–Meier estimates of disease-free survival in the intention-to-treat population according to investigator assessment at the third interim analysis. Tick marks indicate data censored at the last time the participant was known to be alive and free from recurrence. Panel B shows disease-free survival according to key subgroups. Hazard ratios and two-sided 95% confidence intervals were estimated with the use of a stratified Cox regression model for disease-free survival at the third interim analysis.

received by 92.4% of those in the pembrolizumab group (97 of 105) and by 84.8% of those in the placebo group (123 of 145).

### SAFETY

The as-treated population included 488 participants who received at least one dose of adjuvant pembrolizumab and 496 participants who received at least one dose of placebo. Because all the participants had completed or discontinued the trial regimen more than 2 years earlier, the safety findings remained consistent with previous interim analyses (Tables S3, S4, and S5).[12] Adverse events of any cause led to the discontinuation of the trial regimen in more participants in the pembrolizumab group than in the placebo group (103 participants [21.1%] vs. 11 [2.2%]). Pembrolizumab was associated with a higher incidence of serious adverse events of any cause than placebo (20.7% vs. 11.5%), as well as with a higher incidence of adverse events of any grade (79.1% vs. 53.0%) or of grade 3 or 4 (18.6% vs. 1.2%) that were considered by the investigator to be related to pembrolizumab or placebo. No deaths that were attributed to pembrolizumab occurred. A total of 10 treatment-related serious adverse events occurred in the pembrolizumab group beyond 90 days after the discontinuation of trial therapy (Table S6), all of which occurred before 2021.

The incidence of immune-mediated adverse events and infusion reactions (36.5% with pembrolizumab vs. 7.3% with placebo) was consistent with previous reports (Table S7).[12] The median time to the onset of immune-mediated adverse events and infusion reactions was 2.1 months (range, 0.03 to 15.3) in the pembrolizumab group and 4.9 months (range, 0.03 to 12.0) in the placebo group. The median duration of such episodes was 2.9 months (range, 0.03 to 70.7) in the pembrolizumab group and 1.4 months (range, 0.03 to 66.6) in the placebo group; the episodes at 70.7 months and 66.6 months of duration were ongoing as of the data-cutoff date.

**Table 2. Subsequent Anticancer Therapy for Renal-Cell Carcinoma among Participants Who Received Subsequent Therapy (Intention-to-Treat Population).***

| Subsequent Anticancer Therapy | Pembrolizumab (N=132) | Placebo (N=172) |
|---|---|---|
| | *number/total number (percent)* | |
| Drug therapy | 105/132 (79.5) | 145/172 (84.3) |
| Anti–PD-1 or anti–PD-L1 therapy† | 43/105 (41.0) | 101/145 (69.7) |
| VEGF- or VEGF receptor–targeted therapy‡ | 97/105 (92.4) | 123/145 (84.8) |
| Other§ | 32/105 (30.5) | 60/145 (41.4) |
| Radiation therapy | 32/132 (24.2) | 34/172 (19.8) |
| Surgery | 36/132 (27.3) | 50/172 (29.1) |

* Participants were counted once in each applicable row. The sum of each row may exceed the total number of participants because participants could have received multiple types of subsequent anticancer therapy.
† Anti–programmed death 1 (PD-1) or anti–PD-L1 therapy included atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab.
‡ Vascular endothelial growth factor (VEGF)–targeted or VEGF receptor–targeted therapy included axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and tivozanib.
§ Other drug therapy included but was not limited to belzutifan, everolimus, and ipilimumab.

### PARTICIPANT-REPORTED OUTCOMES

The empirical mean changes in the FKSI-DRS scores and EORTC QLQ-C30 physical-functioning scores up to week 260 are shown in Figure S3A and S3B, respectively. Scores in both groups remained generally stable over the reported trial period.

## DISCUSSION

After a median follow-up of 57.2 months, the KEYNOTE-564 trial showed a significant and a clinically meaningful improvement in overall survival with an adjuvant therapy in kidney cancer. Pembrolizumab was associated with a 38% lower risk of death than placebo among participants who were at increased risk for disease recurrence after surgery. The estimated survival curves for the pembrolizumab group and placebo group began separating at 15 months and continued to diverge beyond 2 years of follow-up. Most participants had M0 stage disease at baseline and had efficacy outcomes that were highly similar to those in the overall intention-to-treat population. Survival benefits with pembrolizumab therapy were also seen in a number of subgroups, including in participants who had less-adverse prognostic features, such as M0 stage disease, an ECOG performance-status score of 0, or an absence of sarcomatoid features. The benefit that was associated with pembrolizumab with regard to disease-free survival continued to be observed in the third interim analysis, which was consistent with previous findings.[9,12]

Fewer participants in the pembrolizumab group than in the placebo group received subsequent therapy, which was probably a reflection of the prolonged disease-free survival benefit and fewer relapses with adjuvant pembrolizumab therapy. Among participants with documented recurrence, the percentage of participants who were known to have received any subsequent therapy was similar in the two groups (79.5% with pembrolizumab and 81.4% with placebo). The majority of the recurrence events included distant metastasis (143 of 161 events [88.8%] in the pembrolizumab group and 179 of 210 events [85.2%] in the placebo group). The receipt of treatment after disease relapse was probably for early metastatic disease owing to the close monitoring of trial participants.

Therapy selection and its timing were carried out at the discretion of the treating physician, with consideration given to patient preference, local guidelines, and health status at the time of recurrence. Current first-line treatment options for advanced clear-cell renal-cell carcinoma include combinations of anti–PD-1 plus VEGFR-TKI agents for all International Metastatic Renal-Cell Carcinoma Database Consortium risk groups and an anti–PD-1 plus anti–CTLA-4 combination and VEGFR-TKI monotherapy for specific risk groups.[15-22] Metastasectomy or stereotactic ablative radiotherapy are also reasonable treatment options for patients with oligometastatic disease.[19] With anti–PD-1 or anti–PD-L1 therapy comprising approximately 70% of the subsequent systemic anticancer therapy in the placebo group, subsequent treatment use was consistent with real-world treatment patterns for patients with advanced or metastatic renal-cell carcinoma.[23]

All the participants completed or discontinued the trial regimen by December 2020. Adjuvant pembrolizumab was associated with a higher incidence of adverse events of any grade (79.1%, vs. 53.0% with placebo) and of grade 3 or 4 (18.6% vs. 1.2%) that were attributed to pembrolizumab or placebo during the treatment period and up to 30 days after the discontinuation of the regimen. Treatment-related serious adverse events in the pembrolizumab group were rare during the follow-up period, and none were reported after 2020. The threshold for an acceptable level of toxic effects is much lower with adjuvant treatments than with systemic therapy for advanced disease. A total of 103 participants (21.1%) discontinued pembrolizumab owing to an adverse event, as compared with 11 participants (2.2%) who discontinued placebo. The incidence of discontinuation of pembrolizumab due to toxic effects in the KEYNOTE-564 trial was lower than that observed with certain adjuvant VEGFR-TKIs, including sorafenib, sunitinib, and pazopanib,[3,6,24] but it was not negligible and the safety profile should be taken into consideration in treatment decisions. Although the available questionnaire tools were not designed to detect changes in patient-reported outcomes in the context of adjuvant treatment

and may lack the necessary sensitivity, previously reported and updated participant-reported outcomes in this trial indicate that adjuvant pembrolizumab therapy did not result in a clinically meaningful deterioration in health-related quality of life.[25]

Two other phase 3, double-blind, randomized, placebo-controlled trials showed that neither the combination of nivolumab plus ipilimumab nor atezolizumab monotherapy conferred a disease-free survival benefit.[10,11] In addition, to date, neither trial has presented evidence of a lower risk of death with active drugs than with placebo, given that only 61 deaths have occurred in the CheckMate 914 trial (in 33 of 405 participants in the nivolumab–ipilimumab group and in 28 of 411 in the placebo group) and 107 deaths have occurred in the IMmotion010 trial (in 54 of 390 participants in the atezolizumab group and in 53 of 388 in the placebo group; hazard ratio, 0.97; 95% CI, 0.67 to 1.42) at the last available analysis.[10,11]

Direct comparisons among pembrolizumab, atezolizumab, and nivolumab plus ipilimumab are not available, but several contributing factors have been hypothesized to explain the difference in results between the KEYNOTE-564 trial and the IMmotion010 and CheckMate 914 trials. Individual agents within a drug class have unique properties and molecular features. Combination treatments have a unique side-effect profile in the context of adjuvant therapy.[26-28] In addition, differences in the durations of trial regimens and in the trial populations may have been substantive enough to affect the results.[26,29] The adjuvant nivolumab-plus-ipilimumab regimen in the CheckMate 914 trial was planned to be administered for 6 months, whereas the planned duration of therapy in the KEYNOTE-564 trial was 1 year. In the IMmotion010 trial, an anti–PD-L1 antibody was used, and a small number of participants with non–clear-cell renal-cell carcinoma were enrolled. Furthermore, the proportion of participants with M1 NED status was higher in the IMmotion010 trial than in our trial. Despite these differences, the degree to which such factors affected disease-free survival in each trial is unclear. Overall survival is the standard of efficacy outcomes.[30] The survival improvement that was associated with adjuvant pembrolizumab in the KEYNOTE-564 trial further supports our initial findings with regard to disease-free survival and the usefulness of pembrolizumab in patients with this disease.

Limitations of the current analysis include the small sample sizes and numbers of deaths in some key participant subgroups, which resulted in wide confidence intervals for the estimates of overall survival. Subgroup analyses were hypothesis-generating given that no formal statistical testing was planned. The appropriate strategy for adjuvant treatment should be determined on a case-by-case basis, by weighing efficacy benefits against safety risks, including the possibility of a serious adverse event (reported incidence in this trial, 20.7% in the pembrolizumab group vs. 11.5% in the placebo group) as part of the discussion and informed consent with each patient. Additional data beyond the scope of our analysis are needed to determine key considerations for the subsequent selection of systemic therapy for patients who have disease recurrence with distant metastasis after receiving adjuvant pembrolizumab therapy. In addition, participants who identified their race as Black or as multiple including Black made up 1.9% of the overall trial population, which suggests that they were underrepresented in enrollment.

Although improved disease-free survival has been reported before with adjuvant anti–PD-1 or anti–PD-L1 therapy (e.g., among patients with melanoma[31,32]), our trial also provides evidence of an overall survival benefit with such therapy. Cross-tumor comparisons are very complex owing to the distinct immune responsiveness and tumor microenvironment of different cancers. Of note, the survival benefit with early-line perioperative pembrolizumab therapy was shown in patients with resectable non–small-cell lung cancer in the phase 3 KEYNOTE-671 trial of neoadjuvant pembrolizumab or placebo plus cisplatin-based chemotherapy, followed by adjuvant pembrolizumab or placebo.[33]

This phase 3 trial showed improved overall survival with an adjuvant therapy among patients with clear-cell renal-cell carcinoma who were at increased risk for disease recurrence after nephrectomy with or without metastasectomy. These results further support the use of adjuvant pembrolizumab as a standard intervention after surgery in this disease context.

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## APPENDIX

The authors' full names and academic degrees are as follows: Toni K. Choueiri, M.D., Piotr Tomczak, M.D., Ph.D., Se Hoon Park, M.D., Balaji Venugopal, M.D., Tom Ferguson, M.D., Stefan N. Symeonides, M.D., Ph.D., Jaroslav Hajek, M.U.Dr., Yen-Hwa Chang, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Naveed Sarwar, M.D., Ph.D., Naomi B. Haas, M.D., Howard Gurney, M.B., B.S., Piotr Sawrycki, M.D., Mauricio Mahave, M.D., Marine Gross-Goupil, M.D., Ph.D., Tian Zhang, M.D., John M. Burke, M.D., Gurjyot Doshi, M.D., Bohuslav Melichar, M.D., Evgeniy Kopyltsov, M.D., Ajjai Alva, M.D., Stephane Oudard, M.D., Delphine Topart, M.D., Hans Hammers, M.D., Ph.D., Hiroshi Kitamura, M.D., Ph.D., David F. McDermott, M.D., Adriano Silva, M.D., Eric Winquist, M.D., Jerry Cornell, Ph.D., Aymen Elfiky, M.D., Joseph E. Burgents, Ph.D., Rodolfo F. Perini, M.D., and Thomas Powles, M.D.

The authors' affiliations are as follows: Dana–Farber Cancer Institute and Harvard Medical School (T.K.C.) and Beth Israel Deaconess Medical Center (D.F.M.) — all in Boston; Poznan University of Medical Sciences, Poznan (P.T.), and Provincial Hospital in Torun, Torun (P.S.) — both in Poland; Samsung Medical Center, Sungkyunkwan University School of Medicine (S.H.P.), and Asan Medical Center, University of Ulsan College of Medicine (J.-L.L.) — both in Seoul, South Korea; Beatson West of Scotland Cancer Centre and the University of Glasgow, Glasgow (B.V.), Edinburgh Cancer Centre and the University of Edinburgh, Edinburgh (S.N.S.), and Imperial College Healthcare NHS Trust (N.S.), Barts Health NHS Trust and the Royal Free NHS Foundation Trust, Barts Cancer Institute (T.P.), and Queen Mary University of London (T.P.), London — all in the United Kingdom; Fiona Stanley Hospital, Perth, WA (T.F.), and Maquarie University, Sydney (H.G.) — both in Australia; Fakultní Nemocnice Ostrava, Ostrava (J.H.), and Palacký University and University Hospital Olomouc, Olomouc (B.M.) — all in the Czech Republic; Taipei Veterans General Hospital, Taipei, Taiwan (Y.-H.C.); Abramson Cancer Center, Penn Medicine, Philadelphia (N.B.H.); Fundación Arturo López Pérez, Santiago, Chile (M.M.); University Hospital Bordeaux–Hôpital Saint-André, Bordeaux (M.G.-G.), Hôpital Européen Georges Pompidou, Université Paris Cité, Paris (S.O.), and Centre Hospitalier Universitaire de Montpellier, Montpellier (D.T.) — all in France; the University of Texas Southwestern Medical Center, Dallas (T.Z., H.H.), and Texas Oncology–Houston, Houston (G.D.); Rocky Mountain Cancer Centers, Aurora, CO (J.M.B.); Omsk Clinical Oncology Dispensary, Omsk, Russia (E.K.); the University of Michigan, Ann Arbor (A.A.); the University of Toyama, Toyama, Japan (H.K.); Instituto de Cancer e Transplante de Curitiba, Curitiba, Brazil (A.S.); the London Regional Cancer Program, London Health Sciences Centre, Western University, London, ON, Canada (E.W.); and Merck, Rahway, NJ (J.C., A.E., J.E.B., R.F.P.).

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