# Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial

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## Summary

**Background** Effective adjuvant therapy for patients with resected localised renal cell carcinoma represents an unmet need, with surveillance being the standard of care. We report results from part A of a phase 3, randomised trial that aimed to assess the efficacy and safety of adjuvant nivolumab plus ipilimumab versus placebo.

**Methods** The double-blind, randomised, phase 3 CheckMate 914 trial enrolled patients with localised clear cell renal cell carcinoma who were at high risk of relapse after radical or partial nephrectomy between 4–12 weeks before random assignment. Part A, reported herein, was done in 145 hospitals and cancer centres across 20 countries. Patients were randomly assigned (1:1) to nivolumab (240 mg) intravenously every 2 weeks for 12 doses plus ipilimumab (1 mg/kg) intravenously every 6 weeks for four doses, or matching placebo, via an interactive response technology system. The expected treatment period was 24 weeks, and treatment could be continued until week 36, allowing for treatment delays. Randomisation was stratified by TNM stage and nephrectomy (partial *vs* radical). The primary endpoint was disease-free survival according to masked independent central review; safety was a secondary endpoint. Disease-free survival was analysed in all randomly assigned patients (intention-to-treat population); exposure, safety, and tolerability were analysed in all patients who received at least one dose of study drug (all-treated population). This study is registered with ClinicalTrials.gov, NCT03138512.

**Findings** Between Aug 28, 2017, and March 16, 2021, 816 patients were randomly assigned to receive either adjuvant nivolumab plus ipilimumab (405 patients) or placebo (411 patients). 580 (71%) of 816 patients were male and 236 (29%) patients were female. With a median follow-up of 37·0 months (IQR 31·3–43·7), median disease-free survival was not reached in the nivolumab plus ipilimumab group and was 50·7 months (95% CI 48·1 to not estimable) in the placebo group (hazard ratio 0·92, 95% CI 0·71–1·19; p=0·53). The number of events required for the planned overall survival interim analysis was not reached at the time of the data cutoff, and only 61 events occurred (33 in the nivolumab plus ipilimumab group and 28 in the placebo group). 155 (38%) of 404 patients who received nivolumab plus ipilimumab and 42 (10%) of 407 patients who received placebo had grade 3–5 adverse events. All-cause adverse events of any grade led to discontinuation of nivolumab plus ipilimumab in 129 (32%) of 404 treated patients and of placebo in nine (2%) of 407 treated patients. Four deaths were attributed to treatment with nivolumab plus ipilimumab and no deaths were attributed to treatment with placebo.

**Interpretation** Adjuvant therapy with nivolumab plus ipilimumab did not improve disease-free survival versus placebo in patients with localised renal cell carcinoma at high risk of recurrence after nephrectomy. Our study results do not support this regimen for the adjuvant treatment of renal cell carcinoma.

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## Introduction

The current standard treatment for localised, non-metastatic (stage I–III) renal cell carcinoma is partial or radical nephrectomy.[1,2] Although radical surgical resection of the kidney can be curative for a proportion of patients with localised disease, up to 40% of surgically resected patients with stage II–III disease will eventually relapse, and most will die of metastatic disease.[1–4]

Safe and effective adjuvant treatment options that provide durable disease control and long-term survival benefits are scarce for patients with renal cell carcinoma.[1,2,5] Studies of adjuvant therapy with cytokines, radiotherapy, and vaccine-based regimens did not show benefit, and inconsistent results have been reported with VEGFR-targeted therapies in this setting.[1,5] Despite notable drug-related toxic effects and conflicting results across trials, adjuvant sunitinib is approved in the USA for high-risk patients with renal cell carcinoma based on improved disease-free survival versus placebo in the S-TRAC trial.[6–8]

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See Comment page 796

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## Research in context

### Evidence before this study

Patients with localised renal cell carcinoma who undergo nephrectomy have few adjuvant therapy options that can extend the time they live free of recurrence. We searched PubMed for published clinical trial reports, with no restrictions on language, from Aug 22, 2012, until Aug 22, 2022, using the terms "immunotherapy" OR "immune checkpoint inhibitor", "renal cell carcinoma", and "adjuvant". The identified literature showed that no adjuvant treatments studied showed a significant benefit for both disease-free survival and overall survival in patients with renal cell carcinoma at high risk of recurrence after nephrectomy. The KEYNOTE-564 trial, which evaluated adjuvant pembrolizumab versus placebo in patients with clear cell renal cell carcinoma with an intermediate-to-high risk and high risk of relapse, including a group of patients after metastasectomy and no evidence of disease, was the first trial of an immune checkpoint inhibitor that reported significantly improved disease-free survival, although the overall survival data are not yet mature. The European Association of Urology renal cell carcinoma guideline panel issued a weak recommendation for adjuvant pembrolizumab for patients with high-risk clear cell renal cell carcinoma, until final overall survival data are available. Furthermore, European Society for Medical Oncology clinical practice guidelines similarly recommend that adjuvant pembrolizumab should be considered optional for patients with intermediate-risk or high-risk operable clear cell renal cell carcinoma until overall survival data are reported.

### Added value of this study

In the CheckMate 914 trial (part A), which assessed adjuvant nivolumab plus ipilimumab versus placebo in patients with localised renal cell carcinoma at high risk of recurrence after nephrectomy (median follow-up 37·0 months), we report that the primary endpoint of disease-free survival was not met. Exploratory analyses showed similar outcomes across most subgroups of patients analysed by baseline characteristics of clinical interest. The safety of nivolumab plus ipilimumab in this population was consistent with the known profile for this combination in patients with advanced renal cell carcinoma, although the rate of discontinuation due to treatment-related adverse events was higher with adjuvant nivolumab plus ipilimumab than with placebo in this trial.

### Implications of all the available evidence

Despite previously demonstrated long-term efficacy of dual immune checkpoint inhibition with nivolumab plus ipilimumab in patients with previously untreated advanced renal cell carcinoma, the data from the CheckMate 914 trial do not support a role for this combination as an adjuvant therapy based on dosing and duration of treatment tested for unselected patients with localised renal cell carcinoma at high risk of post-nephrectomy recurrence. The results of our study contrast with those of the KEYNOTE-564 trial, which observed a disease-free survival benefit with adjuvant pembrolizumab. However, consistent with results reported in CheckMate 914, reports from two other phase 3 trials evaluating the use of adjuvant or perioperative immunotherapy in patients with renal cell carcinoma showed no improvements in disease-free survival. In IMmotion010, treatment with adjuvant atezolizumab showed no improvement in disease-free survival versus placebo, nor was there any benefit with perioperative nivolumab versus observation in the PROSPER trial. These findings suggest an ongoing need for continued investigation of perioperative therapeutic approaches to standard surgical management for this patient population with a high unmet medical need.

Immune checkpoint blockade has revolutionised the first-line treatment landscape for patients with advanced renal cell carcinoma. Because of success in advanced disease, substantial interest in exploring immunotherapy regimens in patients with localised renal cell carcinoma has emerged, with the goal of eliminating any residual, undetectable microscopic disease after curative resection.[2,5,8,9] Immune checkpoint inhibitors maintain efficacy after treatment discontinuation, and might eradicate micrometastatic disease.[7,10] Therefore, the efficacy of immune checkpoint inhibitors in patients with advanced disease, together with their ability to provide enduring responses in patients, has provided much of the rationale for evaluation of adjuvant immune checkpoint blockade in patients with localised disease.

Adjuvant pembrolizumab, an anti-programmed death 1 (PD-1) antibody, showed disease-free survival benefits compared with placebo in patients with high-risk clear cell renal cell carcinoma in the prespecified first interim analysis of the KEYNOTE-564 trial, leading to regulatory approval in Europe and the USA.[11–14] However, reports from the IMmotion010 (of adjuvant atezolizumab, a programmed death ligand 1 [PD-L1] inhibitor) and PROSPER RCC (of perioperative nivolumab, a PD-1 inhibitor) trials investigating the use of immunotherapy in patients with renal cell carcinoma have shown no improvement in the primary endpoints of disease-free or recurrence-free survival, respectively.[15,16]

Nivolumab monotherapy has previously shown efficacy as an adjuvant treatment in multiple malignancies, including high-risk muscle-invasive urothelial carcinoma (CheckMate 274),[17] resected oesophageal or gastro-oesophageal junction cancer (CheckMate 577),[18] and stage III–IV melanoma (CheckMate 238).[19] Dual immune checkpoint blockade with nivolumab plus ipilimumab (an inhibitor of cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) has shown significant long-term survival and durable response benefits compared with sunitinib in previously untreated patients with advanced renal cell

carcinoma, supporting evaluation of this combination regimen as an adjuvant treatment for localised disease.[20]

We conducted the phase 3 CheckMate 914 trial to assess disease-free survival by masked independent central review of adjuvant treatment with nivolumab plus ipilimumab versus placebo (primary endpoint in part A of the trial) and adjuvant treatment with nivolumab monotherapy versus placebo (primary endpoint in part B of the trial) in mutually exclusive patients with localised renal cell carcinoma at a high risk of recurrence after radical or partial nephrectomy. The study results for parts A and B will be analysed and reported separately. Herein, we report the results from part A of CheckMate 914.

## Methods

### Study design and participants

CheckMate 914 is a double-blind, randomised, phase 3 trial of adjuvant nivolumab plus ipilimumab versus placebo (part A) and adjuvant nivolumab monotherapy versus placebo (part B). Part A, reported herein, was done in 145 hospitals and cancer centres across 20 countries in North America, South America, Europe, Asia, and Australia.

We recruited adult patients (aged ≥18 years) with localised renal cell carcinoma with a predominantly clear cell histology, at high risk of relapse after partial or radical nephrectomy. Patients had negative surgical margins with no clinical or radiological evidence of macroscopic residual disease or distant metastases (M0) after nephrectomy per local review and confirmed by masked independent central review, and pathological TNM staging pT2a (grade III–IV) N0M0, pT2b (any grade) N0M0, pT3 (any grade) N0M0, pT4 (any grade) N0M0, or pT any (any grade) N1M0.[21] Additional enrolment criteria included an Eastern Cooperative Oncology Group performance status of 1 or less and available tumour tissue for analysis obtained within 3 months before enrolment.

Patients were excluded from the study if they had an active, known, or suspected autoimmune disease or a condition that required systemic treatment with either corticosteroids (>10 mg of prednisone equivalent per day) or other immunosuppressive medications within 14 days before the first dose of study treatment; previous active malignancies within the previous 3 years (except for locally curable cancers that had been apparently cured); received a live or attenuated vaccine within 30 days of first dose of study treatment; or previous systemic therapy for renal cell carcinoma in the neoadjuvant, adjuvant, or metastatic setting. Full eligibility criteria are listed in the protocol (appendix p 11). Sex data were self-reported by study participants. Options of male or female were provided for the participant's sex at birth.

CheckMate 914 was approved by an institutional review board or independent ethics committee and regulatory authorities at each site and done in accordance with Good Clinical Practice guidelines defined by the International Council on Harmonisation, ethical principles underlying European Union Directive 2001/20/EC, and the US code of Federal Regulations Title 21, part 50 (21CFR50). Enrolled patients provided written informed consent according to the principles of the Declaration of Helsinki. Between March 22, 2017, and Feb 13, 2022, five protocol amendments were made, which included changes that affected study design and recruitment (appendix p 10). Full details of the revisions are available in the protocol (appendix p 11).

### Randomisation and masking

In part A of this trial, patients were randomly assigned (1:1) to nivolumab plus ipilimumab or placebo via an interactive response technology system. Randomisation occurred at more than 4 weeks, but 12 weeks or less, after the date of nephrectomy. The Bristol Myers Squibb (Princeton, NJ, USA) interactive response technology group created the computer-generated randomisation schedule; screening of patients was done by study investigators at each site and the random assignment to trial groups was done using an interactive voice response system. Patients were stratified according to pathological TNM staging and Fuhrman nuclear grading categories (pT2a, grade 3 or 4, N0 M0 and pT2b, any grade, N0M0; *vs* pT3, any grade, N0M0; *vs* pT4, any grade, N0M0 and pT any, any grade, N1M0)[21] and type of nephrectomy (partial *vs* radical). Randomisation was done via permuted blocks within each stratum using a block size of two in each treatment group. The study was double-blind; the patients, physicians, physicians' staff, and the study sponsor were masked to treatment assignment, and nivolumab and ipilimumab each had its own matching placebo. The site pharmacist was unmasked to allow preparation of study drug or placebo. Designated staff at Bristol Myers Squibb Research and Development were allowed to be unmasked to treatment before database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A patient's study treatment could be unmasked to the investigator in the event of disease recurrence to determine subsequent treatment, or in the event of a medical emergency or pregnancy, using interactive response technology.

### Procedures

Patients received nivolumab (240 mg) intravenously every 2 weeks for 12 doses and ipilimumab (1 mg/kg) intravenously every 6 weeks (or every third nivolumab dose if dosing was delayed) for four doses, or a matching placebo intravenously at the same frequency as nivolumab and ipilimumab administration. Treatment continued until completion of 12 cycles (12 nivolumab doses and four ipilimumab doses), week 36 of nivolumab treatment, unacceptable toxic effects, recurrence, or withdrawal of consent, whichever occurred first. Dose delays for management of adverse events or SARS-CoV-2 infection, and infusion interruptions or rate changes were allowed for nivolumab, ipilimumab, and placebo; if one drug was to be delayed or discontinued, both study drugs were to be delayed or discontinued. Dose

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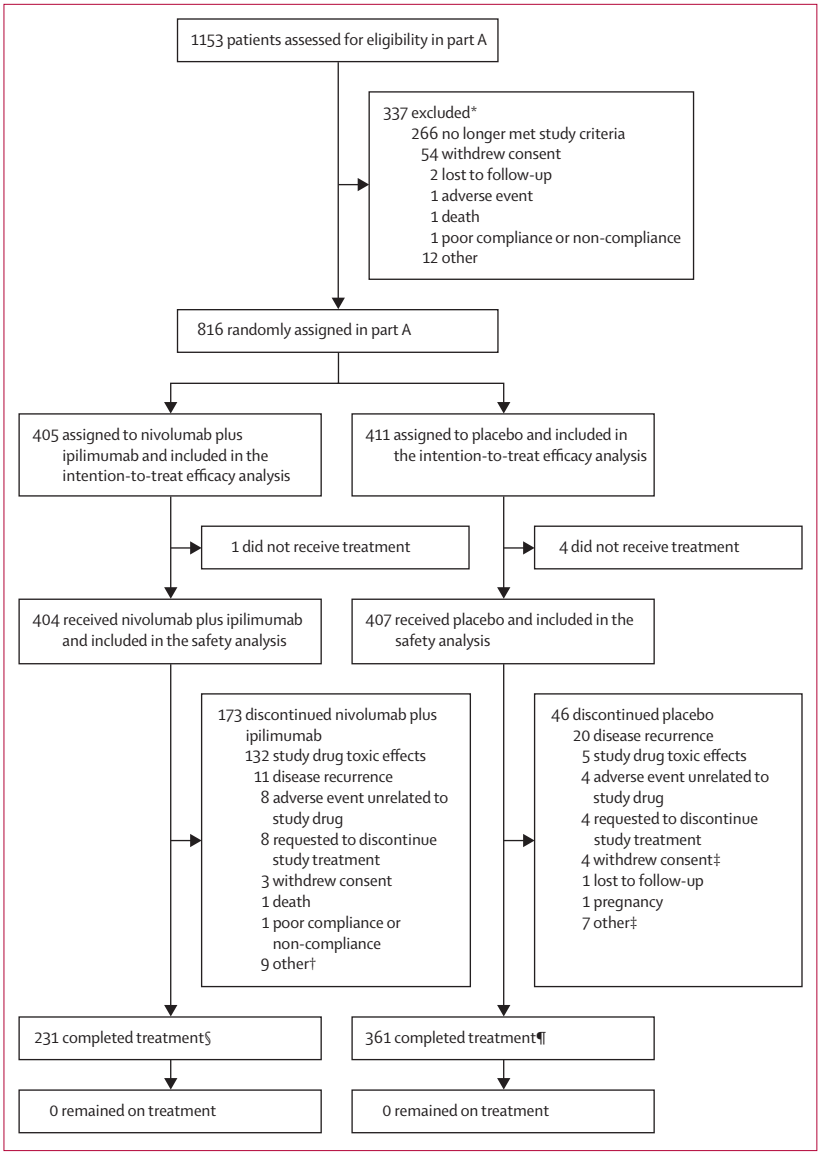


***Figure 1:*** **Trial profile**
*Ten patients were not randomly assigned because of COVID-19. †Nine patients discontinued nivolumab plus ipilimumab because of COVID-19 (all nine patients' reason for discontinuation was labelled as other). ‡Eight patients discontinued placebo because of COVID-19 (one patient withdrew consent; seven patients' reason for discontinuation was labelled as other). §Two patients in the nivolumab plus ipilimumab group were reported to have completed treatment by the investigators even though one patient skipped nivolumab at cycle 3 and one patient skipped nivolumab at cycle 12. ¶One patient in the placebo group was reported to have completed treatment by the investigator even though the patient skipped ipilimumab placebo at cycle 7.

escalations and dose reductions were not allowed for any study drug. All discontinuation criteria applied to nivolumab, ipilimumab, and placebo are detailed in the trial protocol (appendix p 11).

Tumour assessments were done by CT or MRI of the chest, abdomen, and pelvis, and other known or suspected sites of disease. Assessment of disease-free status was done at screening or baseline (greater than 4 weeks post-nephrectomy) and submitted with pre-nephrectomy scans (if available) for confirmation by masked independent central review before random assignment. Subsequent tumour assessments were done at week 23 (±1 week) post-treatment initiation, weeks 36 and 52 (±1 week), then every 6 months (±2 weeks) for years 2–6, then annually to year 10. Tumour assessments were discontinued once recurrence was confirmed by masked independent central review.

## Outcomes

The primary endpoint of CheckMate 914 was disease-free survival according to masked independent central review. Disease-free survival (primary definition) was defined as the time from random assignment to development of local disease recurrence (ie, recurrence of primary tumour in situ or occurrence of a secondary renal cell carcinoma primary cancer), distant metastasis, or death, whichever occurred first. Patients who died without a reported recurrence were considered to have recurred on the date of their death. Disease-free survival was determined based on the disease recurrence date provided by masked independent central review; for patients who received subsequent systemic anticancer therapy, tumour-directed radiotherapy, or tumour-directed surgery, those who received the new therapy before or without a documented recurrence were censored at the date of the last tumour assessment done at or before the initiation of the new therapy. The secondary definition of disease-free survival was similar to the primary definition but excluding censoring for subsequent therapy. The full censoring scheme is provided in the appendix (p 10).

The secondary endpoints were overall survival, safety, and tolerability. Overall survival was defined as the time between the date of random assignment and the date of death. For patients without documentation of death, overall survival was censored on the last date the patient was known to be alive. Safety and tolerability included incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0), timing, seriousness, relatedness, and laboratory abnormalities up to 30 days and 100 days since the final dose of study therapy in all treated patients, defined as patients having received at least one dose of study drug (nivolumab or ipilimumab). Adverse events were collected continuously during treatment. Ongoing treatment-related adverse events were followed up until resolution, return to baseline, or deemed irreversible. Immune-mediated adverse events were reported and defined as events that occurred within 100 days of the final dose, regardless of causality; events treated with immune-modulating medication (except endocrine events, which were considered immune-mediated adverse events regardless of immune-modulating medication administration); events with no clear alternative cause on the basis of investigator assessment; or events with an immune-mediated component. The use of glucocorticoids (≥40 mg prednisone daily or equivalent) to manage these events was also reported.

| | Nivolumab plus ipilimumab (n=405) | Placebo (n=411) |
|---|---|---|
| Age, years | | |
| Median (IQR) | 58 (51–65) | 57 (50–65) |
| <65 | 293 (72%) | 301 (73%) |
| ≥65 | 112 (28%) | 110 (27%) |
| ≥65 to <75 | 93 (83%) | 91 (83%) |
| ≥75 to <85 | 19 (17%) | 19 (17%) |
| Sex | | |
| Male | 286 (71%) | 294 (72%) |
| Female | 119 (29%) | 117 (28%) |
| Race | | |
| White | 302 (75%) | 321 (78%) |
| Black or African American | 3 (1%) | 6 (1%) |
| American Indian or Alaska native | 0 | 3 (1%) |
| Asian | 93 (23%) | 65 (16%) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (<1%) |
| Other | 7 (2%) | 13 (3%) |
| Not reported | 0 | 2 (<1%) |
| Ethnicity | | |
| Hispanic or Latino | 41 (10%) | 44 (11%) |
| Not Hispanic or Latino | 189 (47%) | 198 (48%) |
| Not reported | 175 (43%) | 169 (41%) |
| Region | | |
| USA, Canada, Western Europe, or Northern Europe | 224 (55%) | 240 (58%) |
| Rest of the world | 181 (45%) | 171 (42%) |
| Eastern Cooperative Oncology Group performance status | | |
| 0 | 341 (84%) | 361 (88%) |
| 1 | 64 (16%) | 50 (12%) |
| Type of nephrectomy* | | |
| Radical | 378 (93%) | 381 (93%) |
| Partial | 27 (7%) | 30 (7%) |
| Pathological TNM staging* | | |
| pT2a G3 or G4, N0 M0/pT2b, G any, N0 M0 | 60 (15%) | 62 (15%) |
| pT3, G any, N0 M0 | 315 (78%) | 316 (77%) |
| pT4, G any, N0 M0/pT any, G any, N1 M0 | 30 (7%) | 33 (8%) |
| Disease risk category† | | |
| High | 228 (56%) | 233 (57%) |
| Moderate | 176 (43%) | 177 (43%) |
| Other | 1 (<1%) | 1 (<1%) |
| Fuhrman grade | | |
| Grade 1–2 | 136 (34%) | 147 (36%) |
| Grade 2 | 126 (31%) | 136 (33%) |
| Grade 3 | 189 (47%) | 173 (42%) |
| Grade 4 | 80 (20%) | 91 (22%) |
| (Continued from previous column) | | |
| Sarcomatoid features | | |
| Yes | 19 (5%) | 21 (5%) |
| No | 386 (95%) | 390 (95%) |
| Time from initial disease diagnosis to randomisation <1 year | 405 (100%) | 411 (100%) |
| Lactate dehydrogenase level | | |
| ≤1·5 × ULN | 400 (99%) | 408 (99%) |
| >1·5 × ULN | 0 | 1 (<1%) |
| Not reported | 5 (1%) | 2 (<1%) |
| Haemoglobin | | |
| <LLN | 95 (23%) | 90 (22%) |
| ≥LLN | 310 (77%) | 321 (78%) |
| Corrected calcium, mg/dL | | |
| ≤10 | 368 (91%) | 377 (92%) |
| >10 | 27 (7%) | 17 (4%) |
| Not reported | 10 (2%) | 17 (4%) |
| Alkaline phosphatase | | |
| <ULN | 375 (93%) | 373 (91%) |
| ≥ULN | 29 (7%) | 38 (9%) |
| Not reported | 1 (<1%) | 0 |

Data are n (%), unless otherwise indicated. LLN=lower limit of normal. ULN=upper limit of normal. *According to interactive response technology. †Disease-free survival was assessed in the high-risk and moderate-risk subgroups by using the following risk staging system: high risk (pT3, G3 or G4, N0 M0; pT4, Gany, N0 M0; pTany, Gany, N1 M0) and moderate risk (pT2a, G3 or G4, N0 M0; pT2b, Gany, N0 M0; PT3, G1 and G2, N0 M0).

***Table 1:*** **Demographic and clinical characteristics at baseline in the intention-to-treat population**

The influence of baseline demographic and clinical characteristics on disease-free survival among randomly assigned patients was assessed via exploratory subgroup analyses. The statistical analysis plan prespecified that subgroup analyses for stratification factors (TNM staging and type of nephrectomy) would only be shown using subgroups per case report forms. Exploratory endpoints of CheckMate 914 that are not reported here, and a full listing of exploratory study endpoints, are provided in the protocol (appendix p 11). Assessment of efficacy by PD-L1 expression was part of the exploratory analysis but was ongoing at the time of submission.

## Statistical analysis

We estimated that around 800 patients would be randomly assigned to the study groups. The number of events and power were calculated assuming an exponential distribution and a delayed treatment effect of 3 months. A hierarchical testing procedure was used (disease-free survival, followed by overall survival) with an overall α of 0·05. For the analysis of disease-free survival according to masked independent central review (primary endpoint), around 227 events were expected to provide 90% power to detect a disease-free survival hazard ratio (HR) of 0·65 at an α of 0·05 (two-sided). If the between-group difference in disease-free survival was significant, we specified that overall survival (secondary endpoint) would be tested hierarchically.

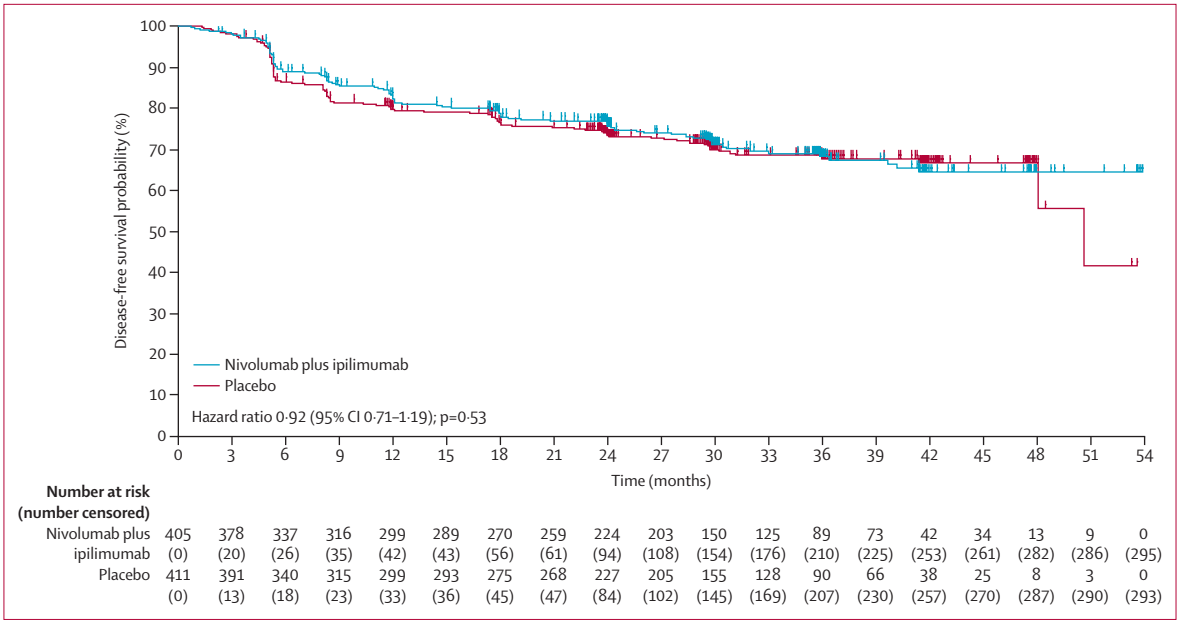


***Figure 2:*** **Kaplan-Meier estimates of disease-free survival (primary definition) according to masked independent central review**
Tick marks represent data censored at the last time that the patient was known to be alive and free from disease recurrence.

Disease-free survival was compared between treatment groups using a two-sided log-rank test stratified by the randomisation stratification factors (ie, pathological TNM staging and type of nephrectomy). HRs and 95% CIs were calculated using a Cox proportional hazards model, with treatment group as the sole covariate, stratified using the same stratification factors. Disease-free survival medians with 95% CIs and rates at fixed timepoints were estimated using Kaplan-Meier methods. Two-sided log-rank p values are reported.

Prespecified exploratory analyses of efficacy endpoints were done in subgroups of demographic and clinical characteristics at baseline, with stratification factors displayed per case report form. Adverse events and events leading to discontinuation of trial treatment or death were summarised descriptively.

Disease-free survival was analysed in all randomly assigned patients (intention-to-treat population); exposure, safety, and tolerability were analysed in all patients who received at least one dose of study drug (all-treated population). A data monitoring committee provided oversight of patient safety and evaluated available efficacy data. All statistical analyses were done with SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT03138512.

### Role of the funding source

The funders of the study contributed to the study design, data analysis, and data interpretation, in collaboration with the authors. The funders did not have a role in data collection. Financial support for editorial and writing assistance was provided by the funders.

## Results

Between Aug 28, 2017, and March 16, 2021, 816 patients were randomly assigned to receive either adjuvant nivolumab plus ipilimumab (405 patients) or placebo (411 patients) in the intention-to-treat population (figure 1). 404 patients received at least one dose of nivolumab plus ipilimumab and 407 patients received at least one dose of placebo and were included in the safety analysis (all treated patients). Baseline demographic and clinical characteristics are shown in table 1. Patient characteristics at baseline were similar across the two study groups. 580 (71%) of 816 patients were male and 236 (29%) patients were female. Most of the enrolled trial population had pathological TNM staging T3 N0M0 (table 1).

As of the clinical data cutoff date on June 28, 2022, 173 (43%) of 404 treated patients in the nivolumab plus ipilimumab group had discontinued study drug without completing treatment, with the most common reason for discontinuation being study drug toxic effects (132 [33%] of 404 treated patients; figure 1). In the placebo group, 46 (11%) of 407 treated patients discontinued study treatment, with the most common reason being disease recurrence (20 [5%] of 407 patients; figure 1). 17 (2%) of 811 treated patients discontinued treatment because of COVID-19 (nine patients in the nivolumab plus ipilimumab group and eight patients in the placebo group). No patients remained on study treatment at the time of writing. 57 (14%) of 405 patients in the nivolumab plus ipilimumab group and 77 (19%) of 411 patients in the placebo group received subsequent systemic therapy; most commonly, a VEGF-targeted agent was used among patients who received subsequent systemic therapy in the nivolumab plus ipilimumab group (55 [96%] of

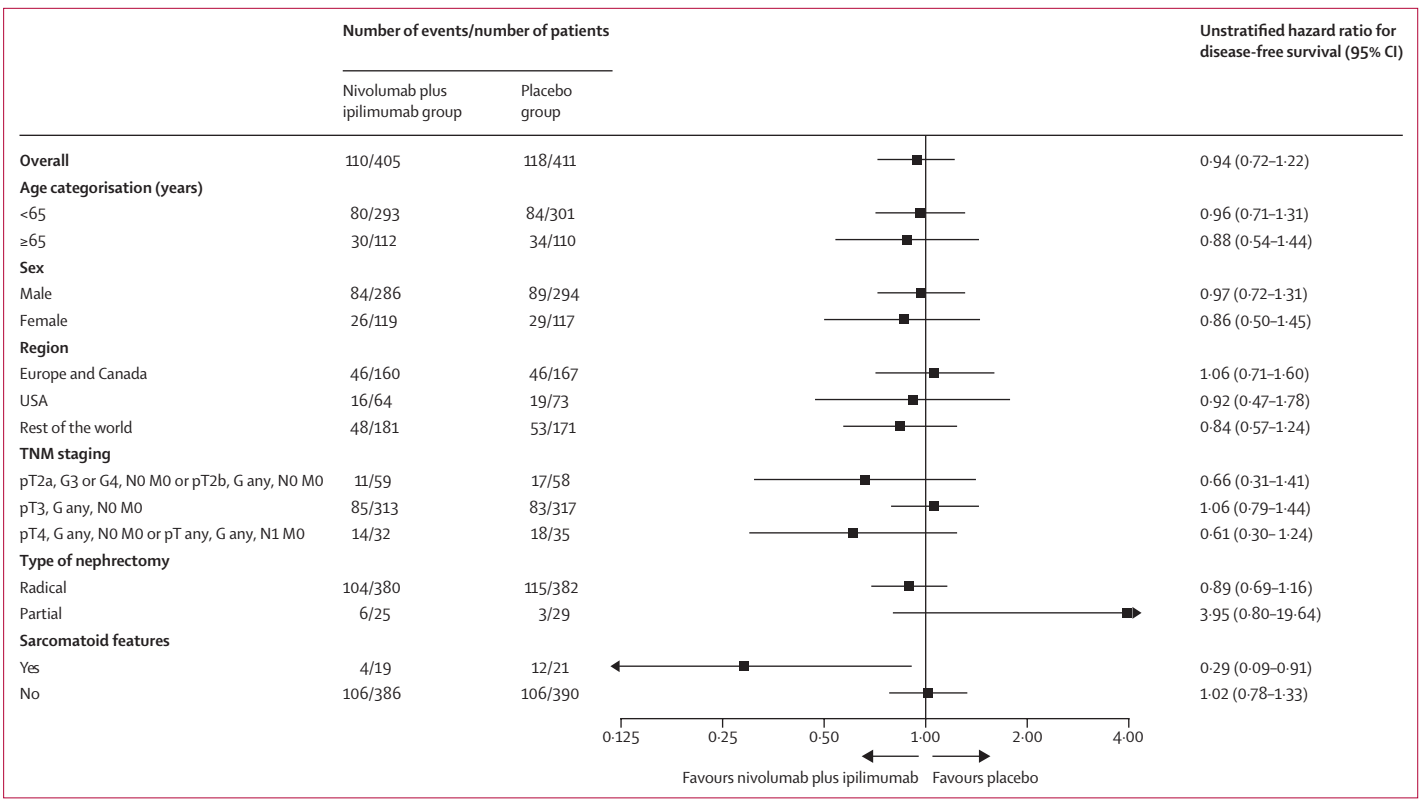


***Figure 3:*** **Disease-free survival according to masked independent central review in key subgroups**
The influence of demographic and baseline clinical characteristics on disease-free survival among randomly assigned patients was assessed via exploratory subgroup analyses. Hazard ratio was not computed for subsets with fewer than 11 patients per treatment group (with the exception of age, region, and sex). The statistical analysis plan prespecified that subgroup analyses for stratification factors (TNM staging and type of nephrectomy) would only be shown using subgroups per case report forms.

57 patients; appendix p 5). In the placebo group, patients most commonly received either a PD1 or PD-L1 inhibitor (53 [69%] of 77 patients) or a VEGF-targeted agent (50 [65%] of 77 patients) as subsequent systemic therapy.

At a median follow-up (time from an individual patient's randomisation date to the date of clinical cutoff [last patient's final visit date for this database lock]) of 37·0 months (IQR 31·3–43·7), 228 events of disease recurrence or death had occurred as assessed by masked independent central review (110 events in the nivolumab plus ipilimumab group and 118 in the placebo group; figure 2). Median disease-free survival was not reached in the nivolumab plus ipilimumab group and was 50·7 months (95% CI 48·1 to not estimable) in the placebo group (figure 2). The risk of disease recurrence or death was not significantly different with adjuvant nivolumab plus ipilimumab than with placebo (HR for recurrence or death 0·92, 95% CI 0·71–1·19; p=0·53). The estimated proportion of patients who remained alive and recurrence-free at 24 months was 76% (95% CI 72–81) in the nivolumab plus ipilimumab group and 74% (69–78) in the placebo group. The corresponding investigator-assessed median disease-free survival was not reached in either study group (HR for recurrence or death 0·92, 95% CI 0·71–1·20; p=0·54), and the proportions of patients who remained alive and recurrence-free at 24 months were 77% (95% CI 73–81) with nivolumab plus ipilimumab and 74% (69–78) with placebo (appendix p 7). The concordance between masked independent central review and investigator assessment for events of recurrence or death and censoring was around 94% in the nivolumab plus ipilimumab group and 99% in the placebo group (figure 2; appendix p 7). Median disease-free survival for the secondary definition of disease-free survival (without censoring for subsequent therapy) was not reached with nivolumab plus ipilimumab (95% CI not estimable) versus 50·7 months (95% CI 48·1 to not estimable) with placebo (HR 0·93, 95% CI 0·72–1·20; p=0·57; appendix p 8).

Exploratory prespecified disease-free survival analyses by stratification factors and other subgroups of clinical interest were performed (figure 3). Across most subgroups, there was no difference between treatment groups. However, disease-free survival favoured nivolumab plus ipilimumab compared with placebo in a small subgroup of 40 patients with sarcomatoid features (HR for disease recurrence or death 0·29, 95% CI 0·09–0·91; figure 3).

The number of events required for the planned overall survival interim analysis was not reached at the time of the data cutoff, and only 61 events occurred (33 in the nivolumab plus ipilimumab group and 28 in the placebo

| | Nivolumab (in nivolumab plus ipilimumab group; n=404) | Ipilimumab (in nivolumab plus ipilimumab group; n=403) | Nivolumab placebo (in placebo group; n=407) | Ipilimumab placebo (in placebo group; n=406) |
|---|---|---|---|---|
| Median number of doses received (range; IQR)* | 12 (1–12; 6–12) | 4 (1–4; 2–4)† | 12 (1–12; 12–12) | 4 (1–4; 4–4)† |
| Last cycle received before treatment period ended | | | | |
| 1 | 17 | 51 | 5 | 8 |
| 2 | 21 | .. | 2 | .. |
| 3 | 14 | .. | 2 | .. |
| 4 | 22 | 50 | 4 | 12 |
| 5 | 16 | .. | 2 | .. |
| 6 | 12 | .. | 5 | .. |
| 7 | 13 | 36 | 6 | 14 |
| 8 | 13 | .. | 3 | .. |
| 9 | 10 | .. | 6 | .. |
| 10 | 12 | 266 | 5 | 372 |
| 11 | 24 | .. | 6 | .. |
| 12‡ | 230 | .. | 361 | .. |
| Patients with at least one dose delay§ | 141 (35%) | 136 (34%) | 110 (27%) | 104 (26%) |
| Relative dose intensity¶ | | | | |
| ≥110% | 0 | 0 | .. | .. |
| 90% to <110% | 332 (82%) | 346 (86%) | .. | .. |
| 70% to <90% | 63 (16%) | 52 (13%) | .. | .. |
| 50% to <70% | 7 (2%) | 4 (1%) | .. | .. |
| <50% | 2 (<1%) | 1 (<1) | .. | .. |

Data are n or n (%), unless otherwise indicated. *Dose units are mg for nivolumab and mg/kg for ipilimumab. †One patient in the nivolumab plus ipilimumab treatment group and one patient in the placebo group did not receive the scheduled dose of ipilimumab or ipilimumab placebo, respectively, at the time that nivolumab or nivolumab placebo was given. ‡One patient in the nivolumab plus ipilimumab group skipped nivolumab at cycle 3 and one patient in the placebo group skipped ipilimumab placebo at cycle 7. §A dose was considered delayed if the delay exceeded 3 days for nivolumab or ipilimumab. ¶Defined as the actual dose received relative to the planned dose.

***Table 2:*** **Treatment exposure and dose delay in all treated patients**

group). Due to immaturity of the overall survival data, Kaplan-Meier estimates of median overall survival were not estimable for both study groups. Kaplan-Meier curves are presented for each study group in the appendix (p 9).

Treatment exposure is summarised in table 2. The median duration of study therapy was 5·1 months (IQR 2·8–5·3; range <0·1–8·3) in the nivolumab plus ipilimumab group and 5·1 months (IQR 5·1–5·3; range <0·1–8·1) in the placebo group. Treated patients in the nivolumab plus ipilimumab group received a median of 12 nivolumab doses (range 1–12; IQR 6·0–12·0) and four ipilimumab doses (range 1–4; IQR 2·0–4·0). In the placebo group, treated patients received a median of 12 nivolumab placebo doses (range 1–12; IQR 12·0–12·0) and four ipilimumab placebo doses (range 1–4; IQR 4·0–4·0). In the nivolumab plus ipilimumab group, 230 (57%) of 404 patients completed all cycles of nivolumab and 266 (66%) of 403 patients completed all cycles of ipilimumab (table 2). In the nivolumab plus ipilimumab group, 141 (35%) of 404 patients had at least one dose delay of nivolumab, and 136 (34%) of 403 patients had at least one dose delay of ipilimumab, with each delay exceeding 3 days. In the placebo group, 110 (27%) of 407 patients had at least one dose delay of nivolumab placebo, and 104 (26%) of 406 patients had at least one dose delay of ipilimumab placebo, each delay exceeding 3 days. Dose delays due to adverse events were attributed to nivolumab in 123 (62%) of 197 total doses delayed, ipilimumab in 44 (26%) of 168 total doses delayed, nivolumab placebo in 45 (31%) of 146 total doses delayed, and ipilimumab placebo in 20 (16%) of 128 doses delayed. Other reasons for dose delays of nivolumab were listed as other (73 [37%] of 197 delays) and not reported (one [<1%] delay). Other reasons for dose delays of ipilimumab were listed as other (30 [18%] of 168 delays) and not reported (94 [56%] delays). Other reasons for dose delays of nivolumab placebo were listed as other (100 [68%] of 146 delays) and not reported (one [1%] delay). Other reasons for dose delays of ipilimumab placebo were other (41 [32%] of 128 delays) and not reported (67 [52%] delays). Other reasons for dose delays included administrative and scheduling issues, the COVID-19 pandemic, and personal reasons.

In the all-treated population, 392 (97%) of 404 patients who received nivolumab plus ipilimumab and 361 (89%) of 407 patients who received placebo had at least one adverse event of any grade and of any cause (table 3).

In the all-treated population, 359 (89%) of 404 patients treated with nivolumab plus ipilimumab and 231 (57%) of 407 patients treated with placebo had at least one treatment-related adverse event of any grade, including an event of grade 3 or 4 in 115 (28%) patients treated with nivolumab plus ipilimumab and eight (2%) patients treated with placebo (appendix p 6). Treatment-related adverse events are listed in the appendix (p 6). Treatment-related adverse events of any grade led to discontinuation of nivolumab plus ipilimumab in 117 (29%) of 404 treated patients and of placebo in four (1%) of 407 treated patients (appendix p 6). The most common treatment-related adverse events leading to discontinuation were diarrhoea (15 [4%] of 404 treated patients), hypophysitis (ten [2%] patients), and increased alanine aminotransferase (ten [2%] patients) in the nivolumab plus ipilimumab group, and increased alanine aminotransferase (one [<1%] of 407 patients), increased aspartate aminotransferase (one [<1%] patient), increased blood creatinine (one [<1%] patient), rash (one [<1%] patient), and eczema (one [<1%] patient) in the placebo group. Four deaths (1% of treated patients in the nivolumab plus ipilimumab group) were attributed to treatment with nivolumab plus ipilimumab and were due to cardiac arrest; immunotherapy-induced diarrhoea or colitis; aortic dissection, ischaemic cerebral infarction, or pulmonary embolism; and drug-induced myocarditis (in one patient each). There were no deaths attributed to treatment with placebo.

93 (23%) of 404 patients treated with nivolumab plus ipilimumab and ten (2%) of 407 patients treated with placebo received corticosteroids (≥40 mg of prednisone daily or equivalent) for any duration of time to manage

immune-mediated adverse events (occurring on therapy or ≤100 days after the end of the trial treatment period); 56 (14%) patients treated with nivolumab plus ipilimumab and four (1%) patients treated with placebo received corticosteroids (≥40 mg of prednisone daily or equivalent) continuously for at least 14 days, and 26 (6%) and one (<1%) patients, respectively, continuously for at least 30 days.

## Discussion

In this phase 3 trial that assessed adjuvant nivolumab plus ipilimumab versus placebo for the treatment of patients with localised renal cell carcinoma who are at high risk of post-nephrectomy recurrence, the primary efficacy endpoint of disease-free survival by masked independent central review was not met. Disease-free survival was also not significantly different between the nivolumab plus ipilimumab and placebo groups, as assessed by the study investigators. Disease-free survival was similar between the treatment groups across most key subgroups. This finding was most prominent in the group of patients with pathological tumour stage T3, which contains a prognostically heterogenous range of pathological tumour features, including invasion of perirenal or renal sinus fat (T3a) to involvement of the vena cava (T3b). As expected, nivolumab plus ipilimumab was associated with higher rates of grade 3–5 adverse events of any cause, treatment-related adverse events, and adverse events leading to treatment discontinuation compared with placebo. However, the overall safety of adjuvant nivolumab plus ipilimumab in patients with localised renal cell carcinoma in this trial was consistent with the known profile for the combination in patients with advanced renal cell carcinoma.[22] Taken together, these results do not indicate a role for the nivolumab plus ipilimumab combination as an adjuvant therapy for patients with high-risk localised renal cell carcinoma according to TNM criteria of post-nephrectomy recurrence. Factors that might have contributed to our reported outcomes include heterogeneity of the patient population studied, the dosing schedule and duration of treatment chosen in this trial, and decreased adverse event tolerability in the setting of adjuvant treatment for localised renal cell carcinoma.

Currently, pembrolizumab is the only immune checkpoint inhibitor approved as an adjuvant therapy for patients with localised renal cell carcinoma after nephrectomy, with specific approval in patients at an increased risk of recurrence after nephrectomy or after nephrectomy and resection of metastatic lesions. This approval was based on data from the phase 3 KEYNOTE-564 trial that compared pembrolizumab monotherapy with placebo.[11] With 24·1 months of median follow-up at a prespecified interim analysis, adjuvant pembrolizumab showed a significant disease-free survival benefit versus placebo.[11] Overall survival in KEYNOTE-564 reported in the primary analysis and with an extended median follow-up of 30·1 months has not shown a significant benefit, although results are immature.[11,12]

Although the results from CheckMate 914 and KEYNOTE-564 might appear conflicting, there are distinctions in the study designs that could have contributed to the divergent outcomes. For instance, differences in the planned and actual duration of therapy might have affected results for each trial. In CheckMate 914, treatment with nivolumab plus ipilimumab was scheduled for 6 months, with an actual median duration of treatment of 5·1 months. In KEYNOTE-564, pembrolizumab treatment was scheduled for around 1 year, with an actual median duration of 11·1 months. Currently, there is no consensus regarding the optimal treatment duration of

| | Nivolumab plus ipilimumab (n=404) | | Placebo (n=407) | |
|---|---|---|---|---|
| | Grade 1–2 | Grade 3–4* | Grade 1–2 | Grade 3–4 |
| **All-cause adverse events** | | | | |
| Patients with any event | 237 (59%) | 154 (38%) | 319 (78%) | 42 (10%) |
| Pruritus | 126 (31%) | 2 (<1%) | 69 (17%) | 0 |
| Fatigue | 120 (30%) | 3 (1%) | 108 (27%) | 1 (<1%) |
| Diarrhoea | 95 (24%) | 16 (4%) | 83 (20%) | 2 (<1%) |
| Rash | 86 (21%) | 5 (1%) | 37 (9%) | 1 (<1%) |
| Headache | 69 (17%) | 2 (<1%) | 59 (14%) | 0 |
| Nausea | 67 (17%) | 2 (<1%) | 50 (12%) | 0 |
| Hyperthyroidism | 65 (16%) | 1 (<1%) | 5 (1%) | 0 |
| Arthralgia | 64 (16%) | 1 (<1%) | 55 (14%) | 0 |
| Hypothyroidism | 63 (16%) | 2 (<1%) | 20 (5%) | 0 |
| Decreased appetite | 51 (13%) | 1 (<1%) | 8 (2%) | 0 |
| Cough | 50 (12%) | 0 | 52 (13%) | 0 |
| Asthenia | 46 (11%) | 2 (<1%) | 31 (8%) | 0 |
| Increased blood creatinine | 45 (11%) | 1 (<1%) | 37 (9%) | 1 (<1%) |
| Increased alanine aminotransferase | 35 (9%) | 10 (2%) | 12 (3%) | 3 (1%) |
| Study treatment discontinuation because of an adverse event† | 47 (12%) | 82 (20%) | 1 (<1%) | 8 (2%) |
| **Immune-mediated adverse events** | | | | |
| Hypothyroidism | 76 (19%) | 2 (<1%) | 13 (3%) | 0 |
| Rash | 61 (15%) | 10 (2%) | 10 (2%) | 2 (<1%) |
| Hyperthyroidism | 62 (15%) | 1 (<1%) | 2 (<1%) | 0 |
| Adrenal insufficiency | 24 (6%) | 11 (3%) | 2 (<1%) | 0 |
| Hypophysitis | 18 (4%) | 12 (3%) | 0 | 0 |
| Diarrhoea or colitis | 15 (4%) | 22 (5%) | 3 (1%) | 0 |
| Hepatitis | 9 (2%) | 14 (3%) | 1 (<1%) | 2 (<1%) |
| Thyroiditis | 9 (2%) | 2 (<1%) | 0 | 0 |
| Pneumonitis | 7 (2%) | 3 (1%) | 1 (<1%) | 0 |
| Nephritis or renal dysfunction | 5 (1%) | 5 (1%) | 5 (1%) | 1 (<1%) |
| Diabetes | 1 (<1%) | 8 (2%) | 0 | 0 |

Data are n (%). Shown are adverse events reported for all treated patients that occurred while patients were receiving the assigned treatment or within 30 days after the last dose of study treatment. Events are listed in descending order of frequency in the nivolumab plus ipilimumab group. *One grade 5 event occurred in the nivolumab plus ipilimumab treatment group. †Includes events reported for all treated patients that led to discontinuation while patients were receiving the assigned treatment or within 30 days after last dose of study treatment.

***Table 3:*** **All-cause adverse events (≥10% cutoff) and immune-mediated adverse events in all treated patients in either treatment group**

adjuvant therapy for patients with localised renal cell carcinoma. The 6-month duration of treatment of nivolumab plus ipilimumab was designed to potentially minimise toxic effects while maintaining expected efficacy, although this might have contributed to the absence of observed activity. Further distinctions between the trials include different screening methods for patient eligibility, stratification factors, primary endpoints, and documentation of disease progression, with KEYNOTE-564 using assessment by investigator versus by investigator with confirmation by masked independent central review in CheckMate 914.[11]

Results from two other phase 3 trials that evaluated the use of adjuvant immunotherapy in patients with renal cell carcinoma showed no improvements in disease-free survival. The IMmotion010 trial[15] evaluated adjuvant checkpoint blockade with atezolizumab in patients with renal cell carcinoma who were at increased risk for recurrence after resection (including patients with both locally advanced intermediate-risk and high-risk M1 NED). With 45 months of median follow-up and a median treatment duration of 10 months, the primary analysis reported no improvement in median disease-free survival versus placebo (57·2 months *vs* 49·5 months; HR 0·93, 95% CI 0·75–1·15; p=0·50).[15] Overall survival was reported with immature follow-up; however, there was no observed trend toward a survival advantage. As the trial was negative for disease-free survival, no formal analysis will be done for overall survival. Treatment-related grade 3–4 adverse events and discontinuation rates were low compared with CheckMate 914.[15] PROSPER is a phase 3, randomised, open-label trial that evaluated priming the immune system with nivolumab before nephrectomy (one dose), followed by adjuvant nivolumab (nine doses) versus surgery alone in patients with high-risk renal cell carcinoma.[16] The primary endpoint of recurrence-free survival was similar in both study groups (HR 0·97, 95% CI 0·74–1·28; p=0·43), with medians not reached. Overall survival was not mature at the time of analysis. The trial was stopped early by the data and safety monitoring committee because of futility.[16]

The primary outcomes of CheckMate 914, IMmotion010, and PROSPER contrast with those of KEYNOTE-564, possibly reflecting differences in the patient populations and dosing schedules, and distinctions in the mechanism of action of the immunotherapy agents tested (anti-PD-1 agents *vs* anti-PD-L1 agents). IMmotion010, PROSPER, and KEYNOTE-564 permitted patients with disease stage M1 with no evidence of disease to enrol in the study, whereas CheckMate 914 did not.[11,15,23] To our knowledge, IMmotion010 and PROSPER are the only trials that permitted patients with non-clear cell histology.[15,23] The length of treatment assessed was predominantly 1 year, with the exception of CheckMate 914, which scheduled treatment for 6 months.[11,15,23] IMmotion010 was the only trial that evaluated a PD-L1 inhibitor (whereas anti-PD-1 inhibitors were studied in CheckMate 914, KEYNOTE-564, and PROSPER).[11,15,23] Overall, PROSPER is difficult to interpret in the context of findings from other phase 3 trials (IMmotion010, CheckMate 914, and KEYNOTE-564) because of substantial differences in trial design.[11,15,23] Future subgroup and biomarker analyses might shed light on benefits in particular patient populations.

In contrast to the results of the CheckMate 914 adjuvant trial (part A), the combination of nivolumab plus ipilimumab has shown substantial efficacy and tolerability compared with sunitinib in patients with untreated advanced renal cell carcinoma and intermediate or poor risk, including long-term survival benefits, durable responses, and a favourable safety profile.[20] The differences in activity observed in the localised (CheckMate 914) and advanced (CheckMate 214) settings might have been brought about by the differences in patient disease characteristics and by adverse event tolerability and treatment discontinuation rates, as well as drug exposure to the nivolumab plus ipilimumab combination.[24] Historically, trials evaluating adjuvant tyrosine kinase inhibitors have shown that a given therapy is not as tolerable in patients with localised disease post-nephrectomy versus when patients have advanced or metastatic disease, leading to increased discontinuation due to adverse events in the former setting.[6,25] Additionally, the extended treatment period for adjuvant ipilimumab compared with the condensed induction regimen in patients with advanced disease might have reduced effectiveness of the CTLA-4 inhibitor without improving tolerability.[22]

The CheckMate 914 trial included two parts, A and B, with each comprising mutually exclusive randomisation schemes and patients. The primary endpoint in part A assessed the efficacy of adjuvant treatment with nivolumab plus ipilimumab versus placebo whereas the primary endpoint in part B will assess adjuvant treatment with nivolumab monotherapy versus placebo. Part B enrolment largely followed that of part A, reported herein, and compares a 6-month course of nivolumab monotherapy with placebo. This trial has completed enrolment and might provide further insight regarding tolerability and the effect of a 6-month treatment programme of checkpoint inhibitor monotherapy as an adjuvant therapy.

A limitation of our study was that the enrolled population was selected on the basis of clinical features, without clear signals for relapse or efficacy based on underlying biology. Furthermore, part A of the CheckMate 914 trial was done in part during the COVID-19 pandemic, with patients randomly assigned between August, 2017, and March, 2021 (clinical data cutoff was June 28, 2022). Patient participation might have been affected by the COVID-19 constraints and implications, such as the ability to travel for continuing treatment or adverse event management, which might have increased the rate of treatment discontinuation.

In conclusion, adjuvant nivolumab plus ipilimumab did not show disease-free survival benefits compared with placebo in patients with localised renal cell carcinoma

who were at high risk of post-nephrectomy recurrence. Patient disease characteristics, adverse events leading to treatment discontinuation, and length of drug exposure might have contributed to the absence of efficacy observed in the trial.

#### Contributors

RJM, PR, VG, YT, BZ, OP, SB, PB, JCG, DY, AL, J-BL, SG, BSh, BSi, JSp, AC, and AB were involved in conceptualisation of the study. RJM, PR, VG, YT, BZ, OP, SB, PB, JCG, DY, AL, J-BL, LA, SG, BSh, JSo, MS, SVE, and AB contributed to the investigation. BSi, JSp, and AC were involved in data curation. BSi was responsible for formal analysis. All authors had full access to all the data in the study. RJM, AB, BSi, JSp, and AC verified all data in the study. All authors wrote, reviewed, and edited the final draft, and had final responsibility for the decision to submit for publication.

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#### Data sharing

Bristol Myers Squibb's policy on data sharing can be found online (https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html). Deidentified and anonymised datasets of clinical trial information, including patient-level data, will be shared with external researchers for proposals that are complete and for which the scientific request is valid and the data are available, consistent with safeguarding patient privacy and informed consent. Upon execution of an agreement, the deidentified and anonymised datasets can be accessed via a secure portal that provides an environment for statistical programming, with R as the programming language. The protocol and statistical analysis plan will also be available. Data will be available for 2 years from the study completion or termination of the programme (July, 2024).

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