Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial

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Summary

Background The first interim analysis of the KEYNOTE-426 study showed superior efficacy of pembrolizumab plus axitinib over sunitinib monotherapy in treatment-naive, advanced renal cell carcinoma. The exploratory analysis with extended follow-up reported here aims to assess long-term efficacy and safety of pembrolizumab plus axitinib versus sunitinib monotherapy in patients with advanced renal cell carcinoma.

Methods In the ongoing, randomised, open-label, phase 3 KEYNOTE-426 study, adults (≥18 years old) with treatment-naive, advanced renal cell carcinoma with clear cell histology were enrolled in 129 sites (hospitals and cancer centres) across 16 countries. Patients were randomly assigned (1:1) to receive 200 mg pembrolizumab intravenously every 3 weeks for up to 35 cycles plus 5 mg axitinib orally twice daily or 50 mg sunitinib monotherapy orally once daily for 4 weeks per 6-week cycle. Randomisation was done using an interactive voice response system or integrated web response system, and was stratified by International Metastatic Renal Cell Carcinoma Database Consortium risk status and geographical region. Primary endpoints were overall survival and progression-free survival in the intention-to-treat population. Since the primary endpoints were met at the first interim analysis, updated data are reported with nominal p values. This study is registered with ClinicalTrials.gov, NCT02853331.

Findings Between Oct 24, 2016, and Jan 24, 2018, 861 patients were randomly assigned to receive pembrolizumab plus axitinib (n=432) or sunitinib monotherapy (n=429). With a median follow-up of 30·6 months (IQR 27·2–34·2), continued clinical benefit was observed with pembrolizumab plus axitinib over sunitinib in terms of overall survival (median not reached with pembrolizumab and axitinib *vs* 35·7 months [95% CI 33·3–not reached] with sunitinib); hazard ratio [HR] 0·68 [95% CI 0·55–0·85], p=0·0003) and progression-free survival (median 15·4 months [12·7–18·9] *vs* 11·1 months [9·1–12·5]; 0·71 [0·60–0·84], p<0·0001). The most frequent (≥10% patients in either group) treatment-related grade 3 or worse adverse events were hypertension (95 [22%] of 429 patients in the pembrolizumab plus axitinib group *vs* 84 [20%] of 425 patients in the sunitinib group), alanine aminotransferase increase (54 [13%] *vs* 11 [3%]), and diarrhoea (46 [11%] *vs* 23 [5%]). No new treatment-related deaths were reported since the first interim analysis.

Interpretation With extended study follow-up, results from KEYNOTE-426 show that pembrolizumab plus axitinib continues to have superior clinical outcomes over sunitinib. These results continue to support the first-line treatment with pembrolizumab plus axitinib as the standard of care of advanced renal cell carcinoma.

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Introduction

Immunotherapy-based drug combinations have transformed the treatment landscape of advanced renal cell carcinoma.[1–3] In treatment-naive patients with advanced renal cell carcinoma, compared with sunitinib, the combination of pembrolizumab, an anti-PD-1 antibody, plus axitinib, a VEGFR inhibitor, showed significant improvements in overall survival, progression-free survival, and the proportion of patients who had a confirmed objective response at a median follow-up of 14·2 months.[1] The benefit of pembrolizumab plus axitinib was observed in the intention-to-treat population and across all predefined subgroups, including International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups.[4] Based on these results, the combination of pembrolizumab plus axitinib is considered a new standard of care for the first-line treatment of advanced renal cell carcinoma.[1,5,6] Because durable response is a hallmark of anti-PD-1 therapy, it is important to understand the benefit of pembrolizumab plus axitinib with longer follow-up.[7]

Overall survival is considered the gold standard in evaluation of clinical outcome, but it requires long periods

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Research in context

Evidence before this study

We did a literature search in PubMed for published clinical trial reports, with no restrictions on article type or language, from database inception until June 8, 2020, using the terms "programmed death-1", "PD-1", "PD-L1", "renal cell carcinoma", "advanced renal cell carcinoma", and "RCC" filtered by the clinical trial article type. Our search found several published randomised studies in patients with treatment-naive advanced renal cell carcinoma that were done to evaluate anti-PD-1 or anti-PD-L1 agents, including phase 3 studies of nivolumab plus ipilimumab, avelumab plus axitinib, atezolizumab plus bevacizumab, and pembrolizumab plus axitinib. These randomised studies use sunitinib monotherapy as control. Consistently, immunotherapy combinations showed improvements in clinical outcomes compared with sunitinib. Atezolizumab plus bevacizumab and avelumab plus axitinib both improved progression-free survival compared with sunitinib, without showing an overall survival benefit, in patients with treatment-naive advanced renal cell carcinoma. The extended follow-up of the initial phase 3 trial of nivolumab plus ipilimumab showed significantly improved overall survival, progression-free survival, and objective responses compared with sunitinib in patients with treatment-naive advanced renal cell carcinoma with intermediate or poor prognostic risk. In the first interim analysis of the randomised, phase 3 KEYNOTE-426 study in patients with treatment-naive advanced renal cell carcinoma, the combination of pembrolizumab, an anti-PD-1 antibody, plus axitinib, VEGFR inhibitor, showed significantly improved overall survival, progression-free survival, and confirmed objective responses compared with sunitinib. Based on these results, the combination of pembrolizumab plus axitinib was approved in the USA, Europe, and other countries worldwide as first-line treatment for patients with advanced renal cell carcinoma.

Added value of this study

With a median follow-up of 30·6 months in this exploratory extended analysis, we report that pembrolizumab plus axitinib continues to show a significant benefit in overall survival, progression-free survival, and confirmed objective response compared with sunitinib.

Implications of all the available evidence

Achievement of an overall survival benefit with combinations of VEGF or VEGFR inhibitor-targeted therapy and immunotherapy has been inconsistent across different regimens in advanced renal cancer. However, with extended follow-up, pembrolizumab plus axitinib continued to show a survival benefit compared with sunitinib. These data continue to support the use of pembrolizumab plus axitinib as standard of care in this setting.

See Online for appendix

of follow-up. Therefore, it is important to identify an early efficacy indictor for long-term survival. Accumulating evidence shows that depth of response, defined as the maximum reduction in target tumour diameter, is associated with long-term survival across a range of advanced malignancies, including metastatic colorectal cancer, non-small-cell lung cancer, and advanced renal cell carcinoma.[8–10] Although Response Evaluation Criteria in Solid Tumors (RECIST) criteria traditionally define four discrete categories (complete response, partial response, stable disease, and progressive disease), depth of response provides a more granular view of response in patients with tumour reduction between 30% and 100%. Therefore, depth of response might be useful in analysing the full spectrum of benefit for some regimens in individual types of cancer. Because RECIST categories might not classify all patients who achieve durable benefit, depth of response might also supplement objective response as an important clinical endpoint.

In this extended follow-up of the KEYNOTE-426 trial, we aimed to assess long-term efficacy and safety of pembrolizumab plus axitinib versus sunitinib monotherapy in patients with advanced renal cell carcinoma.

Methods

Study design and participants

KEYNOTE-426 is an ongoing, phase 3, randomised, open-label trial in treatment-naive advanced renal cell carcinoma, being done in 129 sites (hospitals and cancer centres) in 16 countries (appendix pp 2–6). The trial protocol is available in the appendix. Detailed trial methods have been previously published.[1] Key inclusion criteria were adult patients aged 18 years or older with newly diagnosed stage IV or recurrent renal cell carcinoma with clear cell histology who received no previous systemic treatment for advanced disease. All patients had measurable disease according to RECIST version 1.1[11] and a Karnofsky performance status score of 70 or higher at baseline.[12] Key exclusion criteria were a history of or current symptomatic CNS metastases, active autoimmune disease, poorly controlled hypertension (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg), an ischaemic cardiovascular event or New York Heart Association class III or IV congestive heart failure within 1 year before screening, or if the patient was receiving systemic immunosuppressive treatment. Additionally, patients with a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or meant that it was not in the best interest of the patient to participate, in the opinion of the treating investigator, were excluded.

This study was done in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and the study protocol was approved by the institutional

review boards or ethics committees of all participating sites. All patients provided written informed consent to participate before enrolment.

An independent drug safety monitoring committee (IDMC) evaluated safety and interim efficacy data in accordance with the IDMC charter. Formal statistical testing and the duties of the IDMC ended after results of the first interim analysis showed that the study had achieved both of its dual primary endpoints.

Randomisation and masking

Patients were randomly assigned 1:1 to receive pembrolizumab plus axitinib or sunitinib monotherapy using an interactive voice response system or integrated web response system. Randomisation was stratified by IMDC risk group (favourable *vs* intermediate *vs* poor) and geographical region (North America *vs* western Europe *vs* the rest of the world). Allocation and implementation were managed via the interactive voice response system. There was no masking of treatment assignment in this open-label trial.

Procedures

In the pembrolizumab and axitinib group, 200 mg pembrolizumab was administered intravenously every 3 weeks for up to 35 cycles (approximately 2 years) and 5 mg axitinib was administered orally twice daily (the dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met, and reduced to 3 mg, then 2 mg, twice daily to manage toxic effects); axitinib was to be permanently discontinued if patients could not tolerate 2 mg twice daily. The pembrolizumab dose could also be interrupted because of toxicity. Pembrolizumab could be resumed after the adverse event had been reduced to grade 1 or 0. If corticosteroids were administered at high dose, corticosteroid dose was gradually reduced over a period of 4 weeks. If pembrolizumab was interrupted for reasons other than an adverse event, such as a medical or surgical event, pembrolizumab was administered within 3 weeks of the scheduled interruption. In the sunitinib group, 50 mg sunitinib was administered orally once daily for 4 weeks then off treatment for 2 weeks in 6-week cycles (the dose could be reduced to 37·5 mg, then 25 mg, for the first 4 weeks of each 6-week cycle to manage toxic effects). In both groups, study treatment continued until disease progression, unacceptable toxicity, or patient or investigator decision to discontinue. In the pembrolizumab plus axitinib group, if one of the drugs was discontinued because of toxicity, the other drug could be continued.

Disease assessments were done with CT or MRI at baseline; response evaluations were done at week 12 and then every 6 weeks through week 54 and then every 12 weeks thereafter until disease progression or treatment discontinuation, whichever occurred later. Tumour response was assessed per RECIST version 1.1 by blinded independent central imaging review (BICR). Patient survival status was assessed every 12 weeks during follow-up. Adverse events and laboratory tests for haematology, chemistry, and urinalysis were collected approximately every 3 weeks throughout the treatment period and for 30 days thereafter (data on serious adverse events and events of interest were collected for 90 days after the end of the treatment period). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Adverse events of interest were based on a list of terms specified by the funder and that might be associated with drug exposure and might be consistent with an immune phenomenon that might represent an immunological cause. Subsequent therapies after study treatment discontinuation were permitted per investigator or patient discretion. Full assessment schedules for efficacy and safety have been published previously.[1]

Outcomes

The dual primary endpoints were overall survival and progression-free survival. Overall survival was defined as the time from randomisation to death from any cause. Progression-free survival was defined as the time from randomisation to the first documented disease progression per RECIST version 1.1 based on BICR or death from any cause, whichever occurred first.

Secondary endpoints were objective response (defined as a complete response or partial response) and duration of response (defined as the time from first documented evidence of objective response until disease progression or death from any cause, whichever occurred first) per RECIST version 1.1 as assessed by BICR, and safety and tolerability. Other prespecified secondary endpoints (disease control rate, time to deterioration in the FKSI-DRS scale, and longitudinal changes in the EORTC QLQ-C30 global health status and quality-of-life scale) will be reported in future publications.

Statistical analysis

The current study used a group-sequential design that included two planned interim analyses for overall survival. Details of statistical analyses and results of the first interim analysis (median follow-up 14·2 months [IQR 10·7–17·8]) have been reported previously.[1] The primary and key secondary endpoint (objective response rate per RECIST version 1.1 by BICR) were met at the time of the first interim analysis; therefore, the first interim analysis was also the final alpha-controlled analysis. The planned sample size was 840 participants, but the following power calculations are based on the final number of enrolled and randomly assigned patients (n=861). For the overall survival endpoint, based on a target number of 404 final overall survival events and two interim analyses (with approximately 48% of final overall survival events at the first interim analysis and 74% of the final overall survival events at the second interim analysis), the study has approximately 80% power to detect a hazard ratio

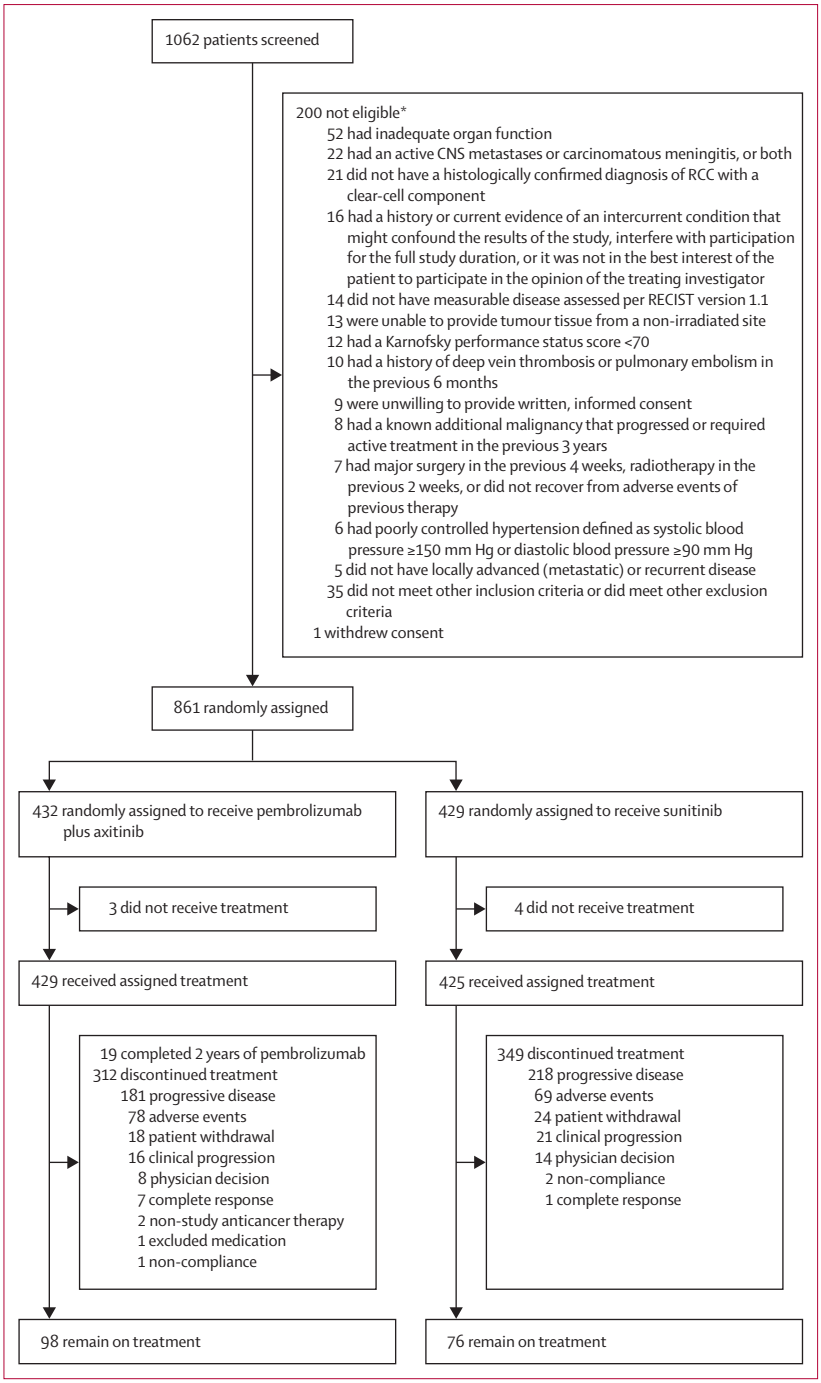

Figure 1: **Trial profile**
RCC=renal cell carcinoma. RECIST=Response Evaluation Criteria in Solid Tumors. *Reasons are not exclusive (ie, one patient can meet more than one criterion).

(HR) of 0·75 at an overall alpha level of 2·3% (1-sided). For the progression-free survival endpoint, based on a target number of 487 events and one interim analysis at approximately 75% of the target number of events, the study has approximately 99% power to detect an HR of 0·60 at an alpha of 0·2% (1-sided).

All efficacy endpoints were analysed using data from the intention-to-treat population; safety was assessed using data from the population of patients who were randomly assigned and received at least one dose of study treatment. Because superiority of pembrolizumab plus axitinib was shown in the first interim analysis of the intention-to-treat population, only nominal p values are reported. Details of statistical analyses for the primary and secondary endpoints were previously reported.[1]

The Kaplan-Meier method was used to estimate progression-free survival, overall survival, and duration of response in each treatment group. The hypotheses of treatment difference were tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate the magnitude of the treatment difference (ie, HR) between the treatment groups. The stratification factors used for randomisation were applied to both the stratified log-rank test and the stratified Cox model. Stratified Miettinen and Nurminen's method with weights proportional to the stratum size was used for comparison of the proportion of patients with an objective response between the treatment groups. For the objective response rate, 95% CIs were based on the binomial exact confidence interval method for binomial data.

To determine whether the treatment effect is consistent across various subgroups, the estimates of the between-group treatment effect (with a nominal 95% CI) for the dual primary endpoints, progression-free survival and overall survival, were estimated and plotted within each subgroup as prespecified in the protocol. The prespecified subgroups are IMDC risk category (favourable *vs* intermediate *vs* poor; favourable *vs* intermediate plus poor), geographic region (North America *vs* western Europe *vs* rest of the world), PD-L1 status (combined positive score [CPS] <1 *vs* CPS ≥1), age (<65 *vs* ≥65), sex (male *vs* female), and race (white *vs* non-white). The post-hoc subgroups are Karnofsky performance status score (90–100 *vs* 70–80) and number of metastatic organs (1 *vs* ≥2). Post-hoc and exploratory analysis of subgroups was done for the proportion of patients who achieved an objective response. Treatment-related adverse events were summarised by descriptive statistics, which were prespecified in the protocol. There were no formal comparisons evaluating incidence of adverse events between the pembrolizumab plus axitinib group and the sunitinib group.

Post-hoc analyses of the association between depth of response (defined as the percentage change in the sum of diameters in target lesions from baseline) and overall survival were done via two methods: stratified Cox proportional hazard model with continuous percentage change in tumour size as a time-varying covariate and landmark analysis with percentage change in tumour size as a categorical variable. Landmark analysis conditionally evaluated the association of overall survival subsequent to the landmark (ie, 6 months after randomisation) and

depth of response status at the landmark (maximum change from baseline to 6 months after randomisation in the sum of diameters of the target lesions) in patients who were alive at the landmark.[13] The non-parametric Kaplan-Meier method was used to estimate the overall survival curve in each treatment group. Seven mutually exclusive categories of depth of response were included: one category was complete response confirmed by BICR per RECIST version 1.1 at the landmark and six categories were based on maximum percentage change in tumour size up to 6 months from baseline by BICR (–100% to –80%, less than –80% to –60%, less than –60% to –30%, less than –30% to less than 0% [reference group], 0% to 20%, and more than 20%). These groups were chosen after clinical input from the trial investigators.

All statistical analyses were done with SAS, version 9.4. This study is registered with ClinicalTrials.gov, number NCT02853331.

Role of the funding source

The funders contributed to the study design, data analysis, and data interpretation in collaboration with the authors. An external data monitoring committee made recommendations about the overall risk and benefit to trial participants. Investigators and site personnel collected data, which was housed on Merck's database. The funder had no role in data collection. All authors had full access to the data. The funder provided financial support for editorial and writing assistance. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

1062 patients were screened for eligibility; 200 patients did not meet the inclusion criteria and one patient withdrew consent before being randomly assigned (figure 1). Between Oct 24, 2016, and Jan 24, 2018, 861 patients were randomly assigned to either the pembrolizumab plus axitinib group (n=432) or the sunitinib monotherapy group (n=429). As of the data cutoff date for the current exploratory extended analysis (Jan 6, 2020), the median follow-up, defined as time from randomisation to database cutoff date, was 30·6 months (IQR 27·2–34·2; range 23·4–38·4). Baseline characteristics of the patients were similar between the two treatment groups (table 1).

At data cutoff, 312 (72%) of 432 patients in the pembrolizumab plus axitinib group and 349 (81%) of 429 patients in the sunitinib group who received at least one dose of study treatment had permanently discontinued treatment. The primary reason for study treatment discontinuation in both groups was radiographic disease progression (figure 1). 19 (4%) of 432 patients in the pembrolizumab plus axitinib group completed the study-defined limit of 35 cycles of pembrolizumab treatment.

Of the patients who discontinued study treatment, 170 (54%) of 312 patients in the pembrolizumab plus axitinib group and 242 (69%) of 349 patients in the sunitinib group received subsequent anticancer therapy (appendix p 7). In both groups, a similar proportion of patients received subsequent VEGF or VEGFR inhibitors, which accounted for 153 (49%) of 312 patients who discontinued study treatment from the pembrolizumab plus axitinib group and 159 of (46%) 349 who discontinued study treatment from the sunitinib group. Only 25 (8%) of 312 patients in the pembrolizumab plus axitinib group received subsequent PD-1 or PD-L1 inhibitors, compared with 169 of (48%) 349 in the sunitinib group.

In the intention-to-treat population, at data cutoff, 320 patients had died: 142 (33%) of 432 patients died in the pembrolizumab plus axitinib group versus

	Pembrolizumab plus axitinib group (n=432)	Sunitinib group (n=429)
Age, years		
Median	62 (55–68)	61 (53–68)
<65	260 (60%)	278 (65%)
Sex		
Male	308 (71%)	320 (75%)
Female	124 (29%)	109 (25%)
Region of enrolment		
North America	104 (24%)	103 (24%)
Western Europe	106 (25%)	104 (24%)
Rest of the world	222 (51%)	222 (52%)
IMDC prognostic risk		
Favourable	138 (32%)	131 (31%)
Intermediate	238 (55%)	246 (57%)
Poor	56 (13%)	52 (12%)
Sarcomatoid features		
Yes	51 (12%)	54 (13%)
No	234 (54%)	239 (56%)
Unknown or missing	147 (34%)	136 (32%)
PD-L1 combined positive score		
≥1	242 (56%)	253 (59%)
<1	165 (38%)	156 (36%)
Missing or unknown	25 (6%)	20 (5%)
Number of organs of metastases		
1	114 (26%)	96 (22%)
≥2	315 (73%)	331 (77%)
Missing	3 (1%)	2 (<1%)
Most common sites of metastasis		
Lung	312 (72%)	309 (72%)
Lymph node	199 (46%)	197 (46%)
Bone	103 (24%)	103 (24%)
Adrenal gland	67 (16%)	76 (18%)
Liver	66 (15%)	71 (17%)
Previous radiotherapy	41 (9%)	40 (9%)
Previous nephrectomy	357 (83%)	358 (83%)

Data are median (IQR) or n (%). IMDC=International Metastatic Renal Cell Carcinoma Database Consortium.

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

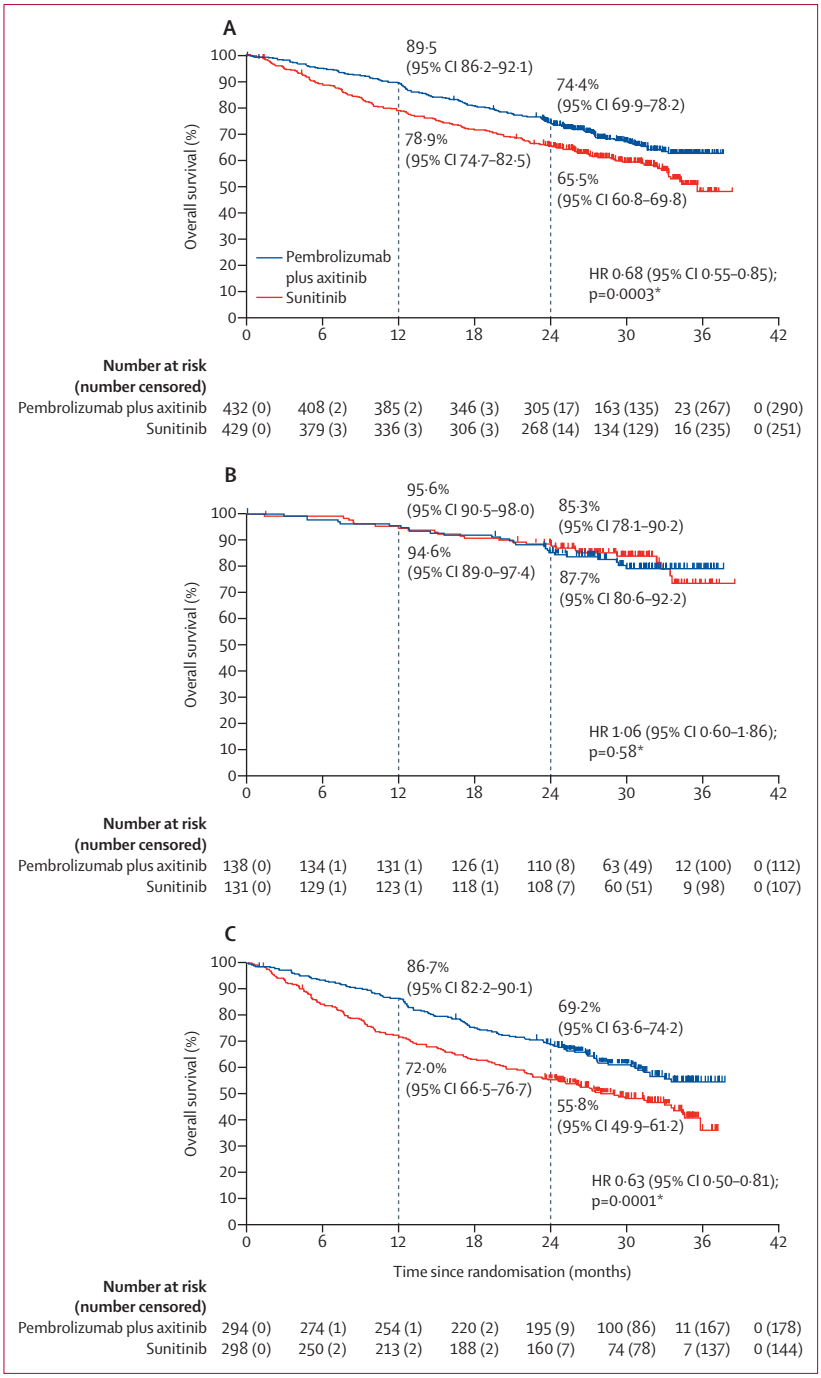

Figure 2: **Kaplan-Meier curves for overall survival**
Overall survival in (A) the intention-to-treat population, (B) patients at International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favourable risk, and (C) patients at IMDC intermediate risk or poor risk. *Because superiority of pembrolizumab plus axitinib was shown at the first interim analysis, no alpha was allocated to overall survival; only nominal p values are reported.

178 (41%) of 429 patients in the sunitinib group. Median overall survival was not reached with pembrolizumab plus axitinib and was 35·7 months (95% CI 33·3–not reached) with sunitinib (HR 0·68, 95% CI 0·55–0·85, p=0·0003; figure 2A). The estimated overall survival rate at 24 months was 74·4% (95% CI 69·9–78·2) in the pembrolizumab plus axitinib group and 65·5% (60·8–69·8) in the sunitinib group. For progression-free survival, 545 patients in the intention-to-treat population had a progression event (disease progression or death): 264 (61%) of 432 patients in the pembrolizumab plus axitinib group versus 281 (66%) of 429 patients in the sunitinib group. Median progression-free survival was 15·4 months (12·7–18·9) with pembrolizumab plus axitinib versus 11·1 months (9·1–12·5) with sunitinib (HR 0·71, 0·60–0·84, p<0·0001; figure 3A). The estimated 24-month progression-free survival rate was higher in patients treated with pembrolizumab plus axitinib (37·6% [95% CI 32·7–42·5]) than in patients treated with sunitinib (26·5% [21·8–31·4]).

Overall survival by IMDC risk category (favourable risk *vs* intermediate or poor risk) is shown in figures 2B and 2C, and the same subgroup analysis of progression-free survival by IMDC risk category is shown in figures 3B and 3C. Overall survival and progression-free survival in the other prespecified and post-hoc patient subgroups is shown in the appendix (pp 10–11).

260 (60%, 95% CI 55·4–64·8) of 432 patients treated with pembrolizumab plus axitinib had a confirmed objective response, compared with 171 (40%, 35·2–44·7) of 429 patients given sunitinib (p<0·0001; table 2). 38 (9%) of 432 patients in the pembrolizumab plus axitinib group and 13 (3%) of 429 patients in the sunitinib group had a complete response. 371 (86%) of 432 of patients treated with pembrolizumab plus axitinib and 332 (77%) of 429 patients treated with sunitinib had some degree of reduction in tumour burden (appendix p 13). In post-hoc subgroup analyses of objective response consistent benefit with pembrolizumab plus axitinib was seen across IMDC risk categories and other subgroups (appendix p 12).

The median duration of response in the intention-to-treat population was 23·5 months (95% CI 19·4–29·0) in the pembrolizumab plus axitinib group and 15·9 months (13·8–20·4) in the sunitinib group (appendix p 14). The estimated percentage of patients with an ongoing response at 24 months was 47% (95% CI 40–54) in the pembrolizumab plus axitinib group and 38% (95% CI 30–47) in the sunitinib group.

In our post-hoc analysis, in the pembrolizumab plus axitinib group, greater tumour reduction was found to be associated with an increase in survival probability (HR 0·85; 95% CI 0·82–0·89) based on the stratified Cox proportional hazard model with continuous percentage change (in the unit of 10%) in tumour size as a time-varying covariate. Results from the post-hoc landmark analysis showed that of the 745 patients who were still alive at 6 months after randomisation, 361 (94%) of 386 patients in the pembrolizumab plus axitinib group and 310 (86%) of 359 patients in the sunitinib group had some degree of tumour reduction within 6 months

of being randomly assigned; 18 (5%) of 386 patients in the pembrolizumab plus axitinib group and four (1%) of 359 patients in the sunitinib group had confirmed complete response at the 6-month landmark (appendix p 8). Kaplan-Meier estimates showed similar overall survival rates in the pembrolizumab plus axitinib group in patients with confirmed complete response per RECIST version 1.1 and those in the –100% to –80% tumour size reduction category (appendix p 15). These results were not observed in the sunitinib group (appendix p 16), although four patients had a confirmed complete response and eight patients had tumour reduction of at least 80%.

No new safety signals emerged with extended follow-up compared with those previously described.[1] Overall, 429 patients received at least one dose of pembrolizumab plus axitinib and 425 patients received at least one dose of sunitinib. 82 (19%) of 429 patients in the pembrolizumab plus axitinib group received a dose escalation of axitinib and one (<1%) of 425 patients in the sunitinib group received a dose escalation of sunitinib from the initial dose. Total exposure of pembrolizumab plus axitinib was 7715·4 person-months and total exposure of sunitinib was 6036·4 person-months. Treatment-related adverse events of any grade occurred in 413 (96%) of 429 patients in the pembrolizumab plus axitinib group and in 415 (98%) of 425 patients in the sunitinib group (table 3). The most frequent (≥10% patients in either group) treatment-related grade 3 or worse adverse events were hypertension (95 [22%] of 429 patients in the pembrolizumab plus axitinib group *vs* 84 [20%] of 425 patients in the sunitinib group), alanine aminotransferase increase (54 [13%] *vs* 11 [3%]), and diarrhoea (46 [11%] *vs* 23 [5%]). Consistent with the first interim analysis, the incidence of grade 3–4 elevations in alanine aminotransferase (54 [13%] of 429 patients) and aspartate aminotransferase (29 [7%] of 429 patients) levels was higher in patients treated with pembrolizumab plus axitinib than previously observed for monotherapy with each drug. After adjusting for exposure, the rate of treatment-related adverse events of any grade was lower with pembrolizumab plus axitinib than with sunitinib (63 events per 100 person-months *vs* 97 events per 100 person-months).

Serious treatment-related adverse events occurred in 122 (28%) of 429 patients in the pembrolizumab plus axitinib group and in 67 (16%) of 425 patients in the group arm. The most common (≥1%) serious treatment-related adverse events in the pembrolizumab plus axitinib group were diarrhoea (11 [3%] of 429 patients), elevated alanine aminotransferase (six [1%]), elevated aspartate aminotransferase (six [1%]), acute kidney injury (five [1%]), pneumonitis (five [1%]), and pulmonary embolism (five [1%]). In the sunitinib group, the most common serious treatment-related adverse event was dehydration (five [1%] of 425 patients).

In the pembrolizumab plus axitinib group, treatment-related adverse events led to pembrolizumab interruption in 188 (44%) of 429 patients, axitinib interruption in 268 (62%), and interruption of both drugs in 129 (30%); treatment-related adverse events led to discontinuation of pembrolizumab in 92 (21%) of 429 patients, discontinuation of axitinib in 84 (20%), and discontinuation of

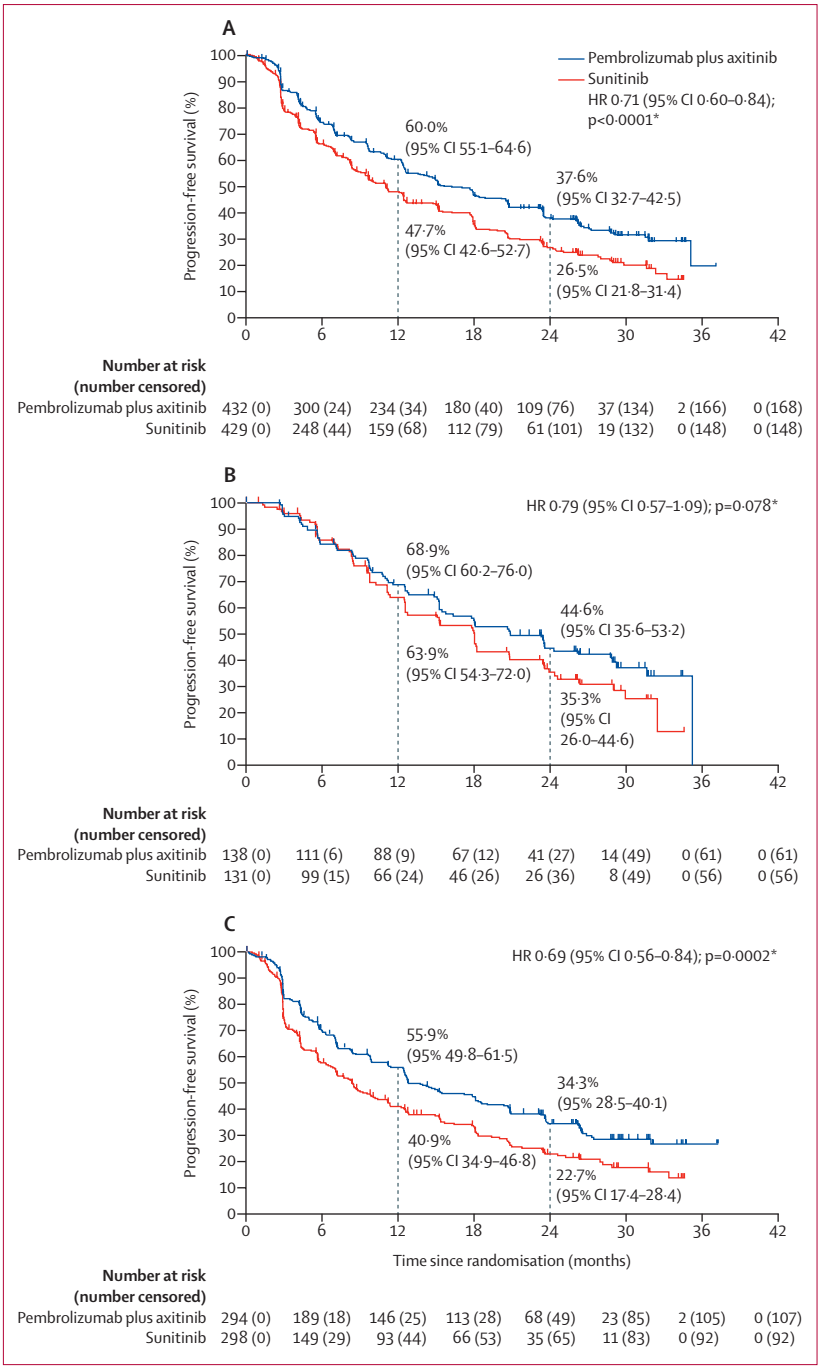

***Figure 3*: Kaplan-Meier curves for progression-free survival**
Progression-free survival in (A) the intention-to-treat population, (B) patients at International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favourable risk, and (C) patients at IMDC intermediate risk or poor risk. *Because superiority of pembrolizumab plus axitinib was shown at the first interim analysis, no alpha was allocated to progression-free survival; only nominal p values are reported.

	Pembrolizumab plus axitinib group (n=432)	Sunitinib group (n=429)
Proportion of patients with confirmed objective response*	260 (60%, 55·4–64·8)	171 (40%, 35·2–44·7)
Best overall response		
Complete response	38 (9%)	13 (3%)
Partial response	222 (51%)	158 (37%)
Stable disease	100 (23%)	150 (35%)
Progressive disease	49 (11%)	74 (17%)
Not assessed†	16 (4%)	28 (7%)
Could not be evaluated‡	7 (2%)	6 (1%)

Data are n (%, 95% CI) or n (%). IMDC=International Metastatic Renal Cell Carcinoma Database Consortium. RECIST=Response Evaluation Criteria in Solid Tumors. *CIs based on binomial exact method for binomial data. †No post-baseline assessment available for response evaluation. ‡Post-baseline assessments available; however, not evaluable (ie, all post-baseline assessments with insufficient data for assessment of response per RECIST version 1.1, or complete response, partial response, or stable disease less than 6 weeks from randomisation).

Table 2: **Best overall response per RECIST version 1.1 criteria by blinded independent central imaging review**

both drugs in 28 (7%). In the sunitinib group, treatment-related adverse events led to interruption in 188 (44%) of 425 patients and discontinuation in 53 (12%).

Grade 3–4 adverse events of interest, which were determined on the basis of a list of terms specified by the sponsor and were considered regardless of whether the investigator determined that they were related to treatment, were more common with pembrolizumab plus axitinib than with sunitinib (53 [12%] of 429 patients vs seven [2%] of 425 patients; appendix p 9). The most common adverse event of interest was hypothyroidism in both the pembrolizumab plus axitinib group (173 [40%] of 429 patients; grade 3 [n=2]) and the sunitinib group (161 [38%] of 425 patients; grade 3 [n=1]).

Deaths from adverse events occurred in 19 (4%) of 429 patients in the pembrolizumab plus axitinib group (acute coronary syndrome, acute myocardial infarction, cardiac failure, cardiac tamponade, myocarditis, unknown cause, general physical health deterioration, sudden cardiac death, necrotising fasciitis, pneumonia, plasma cell myeloma, myasthenia gravis, pleural effusion, pneumonitis, pulmonary embolism, pulmonary thrombosis, and respiratory failure, in one patient each; and cardiac arrest in two patients) and in 17 (4%) of 425 patients in the sunitinib group (cardiac amyloidosis, cardiac arrest, chronic cardiac failure, acute myocardial infarction, gastric haemorrhage, gastrointestinal haemorrhage, unknown cause, sudden death, fulminant hepatitis, sepsis, urinary tract infection, breast cancer, intracranial haemorrhage, shock, and pulmonary embolism, in one patient each; and pneumonia in three patients). No additional treatment-related deaths have been reported since the first interim analysis. Four (1%) of 429 patients died of treatment-related adverse events in the pembrolizumab plus axitinib group (from myasthenia gravis, myocarditis, necrotising fasciitis, and pneumonitis, in one patient each) and six (1%) of 425 patients died of treatment-related adverse events in the sunitinib group (acute myocardial infarction, cardiac arrest, fulminant hepatitis, gastrointestinal haemorrhage, intracranial haemorrhage, and pneumonia, in one patient each).

Discussion

The extended follow-up results of the phase 3 KEYNOTE-426 trial of patients with previously untreated advanced renal cell carcinoma show that treatment with pembrolizumab plus axitinib maintained overall survival, progression-free survival, and objective response benefit compared with sunitinib. Treatment with pembrolizumab plus axitinib resulted in a reduced risk of disease progression or death versus treatment with sunitinib. The overall survival benefit continues to be clinically meaningful despite most patients who discontinued treatment having received subsequent systemic therapy, including 48% of patients in the sunitinib group who received subsequent immunotherapy. Although the confidence intervals are overlapping, a number of factors might account for potential differences between the initial overall survival HR (0·53 [95% CI 0·38–0·74])[1] and the current data (0·68 [0·55–0·85]). These include access to subsequent therapy and greater use of immunotherapy with time. The results presented in this Article probably represent a more mature signal regarding the benefits of pembrolizumab plus axitinib treatment over sunitinib monotherapy, and support that earlier immunotherapy improves survival.

Additionally, it is clinically relevant that 60% of patients treated with pembrolizumab plus axitinib achieved confirmed objective response, compared with 40% of those given sunitinib. The complete response rate of 9% with pembrolizumab plus axitinib with longer follow-up is consistent with observations from other tumour types.[14,15] The safety profiles of pembrolizumab, axitinib, and sunitinib were as expected based on the reported profiles.[5,16,17] No new safety signals were seen and no new treatment-related deaths occurred in either group with longer follow-up.

In subgroup analyses, progression-free survival and objective response benefits with pembrolizumab plus axitinib were generally observed across the various patient subgroups analysed, including IMDC risk categories, but an overall survival benefit within the favourable risk subgroup was not observed in the current analysis. Patients at favourable risk have more indolent disease and biology that are initially more responsive to VEGF-targeted therapy than to immunotherapy.[2] The number of events in this subgroup was relatively small (n=50), and this study was not designed to determine outcomes specifically within any IMDC risk category and therefore did not have adequate power to detect differences between groups. An overall survival benefit from the addition of immunotherapy to VEGF-targeted therapy might require extended follow-up or a study designed with a larger cohort of patients

	Pembrolizumab plus axitinib group (n=429)				Sunitinib group (n=425)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any	126 (29%)	250 (58%)	33 (8%)	4 (1%)	150 (35%)	233 (55%)	26 (6%)	6 (1%)
Diarrhoea	185 (43%)	45 (10%)	1 (<1%)	0	163 (38%)	23 (5%)	0	0
Hypertension	93 (22%)	95 (22%)	0	0	107 (25%)	84 (20%)	0	0
Hypothyroidism	157 (37%)	2 (<1%)	0	0	146 (34%)	0	0	0
Fatigue	128 (30%)	12 (3%)	0	0	128 (30%)	23 (5%)	0	0
Palmar-plantar erythrodysaesthesia	104 (24%)	23 (5%)	0	0	156 (37%)	20 (5%)	0	0
ALT increased	58 (14%)	50 (12%)	4 (1%)	0	47 (11%)	10 (2%)	1 (<1%)	0
AST increased	73 (17%)	27 (6%)	2 (<1%)	0	57 (13%)	7 (2%)	0	0
Decreased appetite	92 (21%)	9 (2%)	0	0	116 (27%)	2 (<1%)	0	0
Dysphonia	98 (23%)	1 (<1%)	0	0	13 (3%)	0	0	0
Nausea	95 (22%)	2 (<1%)	0	0	117 (28%)	4 (1%)	0	0
Proteinuria	69 (16%)	12 (3%)	0	0	39 (9%)	12 (3%)	0	0
Stomatitis	59 (14%)	5 (1%)	0	0	80 (19%)	9 (2%)	0	0
Arthralgia	55 (13%)	3 (1%)	0	0	13 (3%)	2 (<1%)	0	0
Mucosal inflammation	54 (13%)	4 (1%)	0	0	85 (20%)	7 (2%)	0	0
Asthenia	49 (11%)	6 (1%)	0	0	49 (12%)	14 (3%)	0	0
Hyperthyroidism	49 (11%)	4 (1%)	0	0	16 (4%)	0	0	0
Vomiting	39 (9%)	1 (<1%)	0	0	58 (14%)	4 (1%)	0	0
Dysgeusia	33 (8%)	1 (<1%)	0	0	103 (24%)	0	0	0
Platelet count decreased	15 (3%)	0	1 (<1%)	0	48 (11%)	26 (6%)	5 (1%)	0
Anaemia	13 (3%)	0	1 (<1%)	0	63 (15%)	17 (4%)	0	0
Dyspepsia	14 (3%)	0	0	0	48 (11%)	1 (<1%)	0	0
Thrombocytopenia	11 (3%)	0	0	0	76 (18%)	20 (5%)	2 (<1%)	0
Neutropenia	6 (1%)	0	2 (<1%)	0	57 (13%)	29 (7%)	1 (<1%)	0
Leukopenia	5 (1%)	0	0	0	37 (9%)	6 (1%)	0	0
Neutrophil count decreased	4 (1%)	1 (<1%)	0	0	22 (5%)	28 (7%)	2 (<1%)	0
Pneumonitis	13 (3%)	0	0	1 (<1%)	1 (<1%)	0	0	0
Gastrointestinal haemorrhage	2 (<1%)	0	0	0	0	0	0	1 (<1%)
Myasthenia gravis	2 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0	0
Acute myocardial infarction	1 (<1%)	2 (<1%)	0	0	0	0	0	1 (<1%)
Cardiac arrest	0	0	0	0	0	0	0	1 (<1%)
Fulminant hepatitis	0	0	0	0	0	0	0	1 (<1%)
Intracranial haemorrhage	0	0	0	0	0	0	0	1 (<1%)
Myocarditis	0	0	1 (<1%)	1 (<1%)	0	0	0	0
Necrotising fasciitis	0	0	0	1 (<1%)	0	0	0	0
Pneumonia	0	0	0	0	0	1 (<1%)	0	1 (<1%)

Data are n (%). The table shows treatment-related adverse events that occurred in at least 10% of patients in either group, the corresponding grade 3–4 events, and all grade 5 events. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 3: **Treatment-related adverse events in the safety population**

with favourable-risk disease.[18] However, the current progression-free survival and objective response data are encouraging. The progression-free survival curve in the favourable IMDC subgroup began to separate after 12 months. Notably, 70% of patients with favourable-risk disease in the pembrolizumab plus axitinib arm achieved an objective response compared with 50% of patients in the sunitinib group. The benefits observed with pembrolizumab plus axitinib in progression-free survival and objective response therefore offer support for use of this regimen in this favourable subset. Further follow-up for this population is ongoing.

Results of other phase 3 trials in advanced renal cell carcinoma that were done to compare immune checkpoint inhibitor-based combinations with sunitinib have also shown clinical benefit, but the extent of benefit has differed among endpoints and studies.[3,19,20] Avelumab plus axitinib improved progression-free survival compared with sunitinib, but overall survival was not reported despite similar follow-up to the pembrolizumab plus axitinib data presented here.[3] A similar pattern was reported for atezolizumab plus bevacizumab.[19] Final overall survival analyses on these studies are awaited. Extended follow-up with nivolumab plus ipilimumab in

the CheckMate 214 study[20] showed continued improvement in overall survival and objective responses compared with sunitinib in patients with IMDC intermediate risk or poor risk. Overall survival was similar between groups for patients in the IMDC favourable risk subgroup, although a greater proportion of patients had an objective response with sunitinib (50%) than with nivolumab plus ipilimumab (39%).[20]

A post-hoc analysis in this study was done to investigate the relationship between depth of response and overall survival. Consistently, both tumour size change as a continuous time-varying covariate and as a categorical endpoint indicated that change in tumour size was a prognostic factor of overall survival. Results of the continuous scale showed that each 10% reduction in tumour size might result an increase in survival probability. Results using the categorical scale also showed that patients in the pembrolizumab plus axitinib group with an at least 80% reduction in target lesions within 6 months of randomisation had a durable subsequent overall survival benefit (ie, 36-months survival), similar to patients who had RECIST-defined complete response. These data support a hypothesis that durable benefit to an immunotherapy-containing regimen in renal cell cancer is not limited to the subset of complete responders, as defined by RECIST version 1.1. The definition of complete response does not seem to encapsulate all patients who have a durable benefit with pembrolizumab plus axitinib therapy. Residual disease might also be difficult to distinguish from normal tissue, making an accurate assessment of complete response difficult.[11] In the CheckMate 214 study,[21] patients who received nivolumab plus ipilimumab and had a tumour burden reduction of 50% to 75% had similar overall survival as those who had more than a 75% reduction. Studies focusing on other cancers such as melanoma have shown similar findings supporting the hypothesis that durable benefit is not confined to patients who had RECIST-defined complete response.[22] These results indicate that responses by RECIST version 1.1 guidelines might not be capturing the spectrum of clinical outcomes, and a more nuanced approach to evaluation of treatment benefit could be useful. Notably however, boundary cutpoints in this exploratory analysis were not prespecified and might not represent the optimal cutpoints for categorisation. It is also difficult to ascertain the roles of pembrolizumab and axitinib in early tumour volume reduction, and, in turn, the degree to which each agent is associated with depth of response. Further investigation is necessary to evaluate depth of response as an endpoint, how outcomes compare with responses measured using RECIST guidelines, and if baseline tumour size affects survival. Because clinical outcomes in renal cell carcinoma might be associated with improved quality of life, health-related quality of life in KEYNOTE-426 will be reported in a separate manuscript, and future analyses evaluating the association between depth of response and quality of life are planned.[23,24]

This study has several important limitations. The first interim results of the study, favouring pembrolizumab plus axitinib, were broadcast during the period of follow-up of this dataset, which might have influenced treatment decision making. This study was also not adequately powered for subgroup analysis. The depth of response analysis was exploratory and limited by the small number of patients who achieved a complete response within 6 months of randomisation. Furthermore, data regarding the outcomes of patients who discontinued either or both pembrolizumab and axitinib, including patients who received the protocol-defined maximum 35 pembrolizumab doses, are not available to estimate the durability of benefit of this regimen after treatment cessation.

Overall, the results of this study continue to support pembrolizumab plus axitinib as standard of care in patients with previously untreated advanced renal cell carcinoma.

Contributors

ERP, VS, LRM, MBA, and BIR contributed to conception and design of the study. TW, RG, FP, BM, IV, DB, JB, and ST contributed to data acquisition. TP, ERP, DS, TW, RG, FP, SJA, DB, ST, LY, MC, MBA, and BIR contributed to data analysis. TP, ERP, DS, TW, RG, DN, FP, BM, SJA, DB, RSM, JB, ST, LY, MC, MBA, and BIR contributed to data interpretation. TP, ERP, TW, VS, RG, DN, ST, MC, LRM, MBA, and BIR contributed to drafting the manuscript. TP, ERP, DS, TW, RG, DN, FP, BM, IV, SJA, DB, RSM, JB, ST, LY, MC, LRM, MBA, and BIR contributed to revising the manuscript All authors provided final approval to submit the manuscript for publication.

Declaration of interests

TP reports research funding from AstraZeneca, Roche, Bristol-Myers Squibb, Exelixis, Ipsen, Merck Sharp & Dohme, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; honoraria from Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, and Roche; and travel accommodation from Roche, Pfizer, Merck Sharp & Dohme, AstraZeneca, and Ipsen. ERP reports research funding for clinical trials from Merck Sharp & Dohme, AstraZeneca, Bristol-Myers Squibb, Peloton, Pfizer, and Astellas; has been a consultant or adviser for AstraZeneca, Bristol-Myers Squibb, Genentech, Merck, Pfizer, Clovis, Exelixis, Incyte, Seattle Genetics, Janssen, Flatiron Health, Infinity Pharma, and McKesson; honoraria for continuing medical education-certified presentations from the American Urological Association, Clinical Care Options, Fox Chase Cancer Center, Georgetown, American Society of Clinical Oncology, Medscape, Icahn School of Medicine at Mount Sinai, National Comprehensive Cancer Network, Omniprex, OncLive, Physicians' Education Resource, PriME Oncology, Research to Practice, Spire Learning, the University of Pennsylvania, Thomas Jefferson University, and the University of Michigan; and has a patent pending for methods for screening muscle-invasive bladder cancer patients for neoadjuvant chemotherapy responsiveness. DS reports research funding to their institution from Merck, Bristol-Myers Squibb, and GlaxoSmithKline; and advisory role for Merck, Bristol-Myers Squibb, Eisai, Ipsen, and Pfizer. TW reports research funding from Bristol-Myers Squibb, Pfizer, and Ipsen; honoraria from Bristol-Myers Squibb, Pfizer, and EUSA Pharma; travel expenses from Bristol-Myers Squibb, EUSA Pharma, and Ipsen; serving on advisory boards for Bristol-Myers Squibb, Pfizer, Ipsen, and Eisai; and a research grant from Merck Sharp & Dohme. DN reports personal fees from lectures for Bristol-Myers Squibb, Sanofi, Bayer, Exelixis and has been a consultant for Merck Sharp & Dohme. BM reports honoraria from and served on advisory boards for Merck Sharp & Dohme, Pfizer, Bristol-Myers Squibb, Merck Serono, Novartis, Eisai, Bayer, and Roche and has received travel expenses from Bristol-Myers Squibb and Pfizer. DB reports research funding from Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer, Roche, Exelixis, and Calithera; has been a consultant for Pfizer, Roche, Ipsen, Novartis,

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Data sharing

The data sharing policy for Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc (Kenilworth, NJ, USA), including restrictions, is available on the Engagezone website. Requests for access to the clinical study data can be submitted through the Engagezone website or via email to dataaccess@merck.com.

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