



Original Research

Axitinib plus pembrolizumab in patients with advanced renal-cell carcinoma: Long-term efficacy and safety from a phase Ib trial



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Received 18 November 2020; accepted 1 December 2020

Available online 4 January 2021

KEYWORDS

Axitinib;
Pembrolizumab;

Abstract Background: Axitinib plus pembrolizumab showed superior overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) versus sunitinib in a randomised phase III trial in patients with advanced renal-cell carcinoma (RCC). We report

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Long-term;
Progression-free
survival;
Overall survival;
Renal-cell carcinoma;
Safety

long-term efficacy and safety of the axitinib/pembrolizumab from the phase I trial (NCT02133742), after 46–55 months from study initiation (data cut-off date, 23rd July 2019).

Methods: Fifty-two treatment-naïve patients with advanced RCC were treated with oral axitinib 5 mg twice daily and intravenous pembrolizumab 2 mg/kg every 3 weeks. PFS, duration of response (DoR) and OS were summarised using the Kaplan–Meier method.

Results: At a median follow-up of 42.7 months (95% confidence interval [CI]: 41.1–44.1), median OS was not reached; 38 (73.1%) patients were alive. The probability of being alive at 4 years was 66.8% (95% CI: 49.1–79.5). Median PFS in the overall population was 23.5 months (95% CI: 15.4–30.4). ORR was 73.1%; five patients had complete response. Median DoR was 22.1 months (95% CI: 15.1–34.5). Grade III/IV adverse events (AEs) were reported in 38 (73.1%) patients and 20 (38.5%) discontinued treatment because of AEs: 17 (32.7%) discontinued axitinib, 13 (25.0%) discontinued pembrolizumab, and 10 (19.2%) discontinued both drugs. Common AEs included diarrhoea (84.6%), fatigue (80.8%), hypertension (53.8%), cough (48.1%) and dysphonia (48.1%). There were no new AE terms reported and no treatment-related deaths.

Conclusions: In patients with advanced RCC with ~4 years of follow-up, combination axitinib/pembrolizumab continued to demonstrate clinical benefit, with no new safety signals.

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1. Introduction

Renal-cell carcinoma (RCC) is the most common form of kidney cancer, with ~400,000 new cases diagnosed worldwide each year [1]. Until recently, inhibitors of the vascular endothelial growth factor (VEGF) pathway were the mainstay of treatment for patients with advanced RCC. However, treatment resistance eventually develops while patients are on therapy. Immune checkpoint inhibitors have also demonstrated anti-tumour activity in patients with advanced RCC [2–5]. Although durable responses have been observed, the response rates and median progression-free survival (PFS) observed with single-agent programmed cell death protein 1 (PD-1) pathway inhibitors have generally been less than that typically seen in patients treated with VEGF pathway inhibitors [2,3,5–7].

Strategies to enhance efficacy include the combination of antiangiogenic agents with immune checkpoint inhibitors. Axitinib is a selective inhibitor of the VEGF receptors 1–3 [8]; pembrolizumab is a monoclonal antibody targeting PD-1 [9]. Both drugs demonstrated antitumour activity as monotherapy in treatment-naïve patients with advanced RCC [2,6,7]. In a phase I trial of axitinib plus pembrolizumab, at a median follow-up of 20.4 months, 73.1% of patients had objective response, median PFS was 20.9 months (95% confidence interval [CI]: 15.4–not evaluable [NE]), median duration of response (DoR) was 18.6 months (95% CI: 15.1–NE), and median overall survival (OS) was not reached [10]. This data prompted a randomised phase III trial in advanced RCC, in which axitinib plus pembrolizumab, compared with sunitinib, showed superior OS (hazard ratio [HR] = 0.53, 95% CI: 0.38–0.74, $p < 0.0001$), PFS (HR = 0.69, 95% CI: 0.57–0.84, $p < 0.001$), and

objective response rate (ORR; 59.3% versus 35.7%, $p < 0.001$) [11]. Among responders, the median DoR was not reached with axitinib plus pembrolizumab and 15.2 months with sunitinib; 70.6% of patients treated with axitinib plus pembrolizumab and 61.6% treated with sunitinib were estimated to have an ongoing response at 1 year [11]. Based on this trial, the combination of axitinib plus pembrolizumab is now approved in the United States and Europe and is a commonly chosen first-line treatment option for patients with advanced RCC [9,12].

Recently, the phase III trial data were updated to a minimum follow-up of 23 months and the combination of axitinib plus pembrolizumab continues to show improved OS (HR = 0.68, 95% CI: 0.55–0.85; $p < 0.001$), PFS (HR = 0.71, 95% CI: 0.60–0.84; $p < 0.001$), and ORR (60.0% versus 40.0%; $p < 0.0001$) compared with sunitinib [13]. As these data are still maturing, the best indications of long-term efficacy for this combination can be found from the phase I trial. Here, we report long-term efficacy and safety data of axitinib plus pembrolizumab from the phase I trial, after 46–55 months from study enrolment.

2. Methods

2.1. Study design and patients

Patients and the study design have been reported previously [10]. Briefly, this was an open-label, phase Ib, multicenter study (NCT02133742) to evaluate the efficacy and safety of axitinib plus pembrolizumab. Overall, 52 treatment-naïve patients with advanced RCC were enrolled between 23rd September 2014 and 13th October 2015. Key eligibility criteria included

histologically or cytologically confirmed clear-cell advanced RCC with primary tumour resected; at least one measurable lesion, defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; Eastern Cooperative Oncology Group performance status 0 or 1; and controlled hypertension.

Patients were treated with oral axitinib 5 mg twice daily and intravenous pembrolizumab 2 mg/kg every 3 weeks. Planned treatment duration was 2 years for pembrolizumab and not limited for axitinib. This study was conducted in compliance with the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. All patients provided written informed consent.

2.2. Efficacy and safety assessments

Tumours were assessed by the investigators at each site, using RECIST, at baseline (screening), 12 weeks, every 6 weeks thereafter until week 66, and then every 12 weeks until the end of study treatment. Safety assessments included adverse events (AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

2.3. Statistical analysis

PFS, DoR and OS were summarised using the Kaplan–Meier method. Medians and two-sided 95% CIs were calculated using the Brookmeyer and Crowley method. Objective response was defined as proportion of patients who achieved complete response or partial response according to RECIST v1.1. OS was defined as the time from first dose of pembrolizumab to date of death due to any cause. PFS and DoR data were censored on the date of the last evaluable tumour assessment documenting absence of progressive disease in patients who were alive and progression-free at the time of the analysis, had documentation of disease progression or death on study after two or more consecutive missed tumour assessments, discontinued treatment because of toxicity, or received antitumour treatment other than the study medication before documented disease progression or death.

Landmark *ad hoc*, exploratory analyses of OS and DoR by time on axitinib treatment were conducted. For the OS analysis, patients still alive at ≥ 1 year were divided into two groups: those still on axitinib treatment and those who were not. For the DoR analysis, patients who were responders and still alive at ≥ 6 months were divided into two groups: those still on axitinib treatment and those who were not.

OS follow-up time in months was calculated as Eq (1)

$$([\text{date of death, or date of last contact if alive}] \text{ minus start date} + 1) / 30.44. \quad (1)$$

Analysis of OS follow-up time by the reverse Kaplan–Meier method was based on the Brookmeyer and Crowley method. Because of protocol amendment to stop collection of tumour assessments every 12 weeks and defer to standard-of-care assessments after the primary analysis, there are limited data beyond 36 months, which was the last time point with meaningful risk set. The data cut-off date for these updated analyses was July 23, 2019.

3. Results

3.1. Patients

As previously reported [10], the median age was 63.0 years, and most patients were male (78.8%) and white (86.5%). Based on International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, 46.2%, 44.2% and 5.8% of patients were reported as having favourable, intermediate and poor risk, respectively, and the risk was unknown in 3.8% of patients.

3.2. Efficacy

At the data cut-off date, with a median follow-up of 42.7 months (95% CI: 41.1–44.1; range 3.0–54.9), median OS was not reached (Fig. 1A), 38 (73.1%) patients were alive, and 14 (26.9%) had died. No deaths were related to treatment. Of the 38 patients who were still alive, 30 (78.9%) were previous responders and 11 (28.9%) were still receiving study treatment. The probability of being event-free (PFS or OS) at 1, 2, 3, and 4 years is shown in Figs. 1A and 2A. OS by the IMDC risk group is shown in Fig. 1B. The probability of survival at 3 years in patients with favourable, intermediate and intermediate + poor risk was 87.5%, 81.6% and 75.8%, respectively. Median PFS was 23.5 months (95% CI: 15.4–30.4); 27.7% of patients were progression-free at 3 years (Fig. 2A). PFS by the IMDC risk group is shown in Fig. 2B.

ORR was 73.1% (95% CI: 59.0%–84.4%). Five patients had complete response, and all five remained alive; three were still on treatment (one each on pembrolizumab, axitinib, and axitinib plus pembrolizumab [re-challenged after disease progression on axitinib monotherapy]), and two patients stopped treatment. ORR (95% CI) in patients with favourable, intermediate and intermediate + poor-risk groups, respectively, were 75.0% (53.3%–90.2%), 69.6% (47.1%–86.8%) and 69.2% (48.2%–85.7%). Landmark analyses of OS (Fig. 3A) and DoR (Fig. 3B) by time on axitinib treatment showed clear separation between the groups, favouring those who were still on axitinib treatment at ≥ 1 year and ≥ 6 months, respectively.

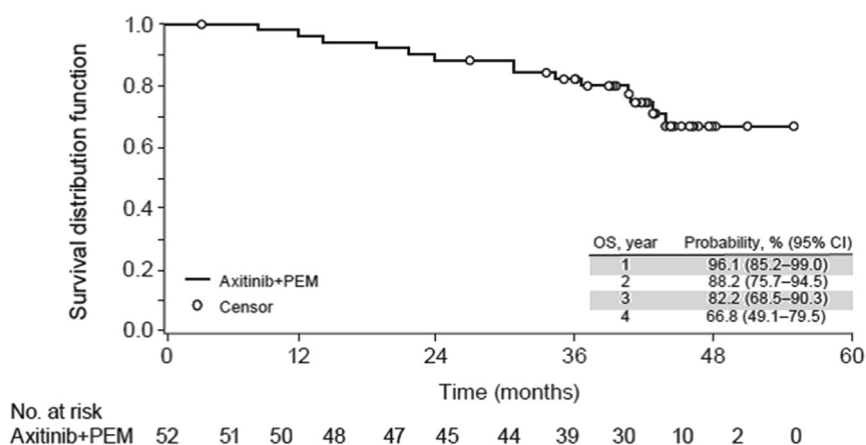
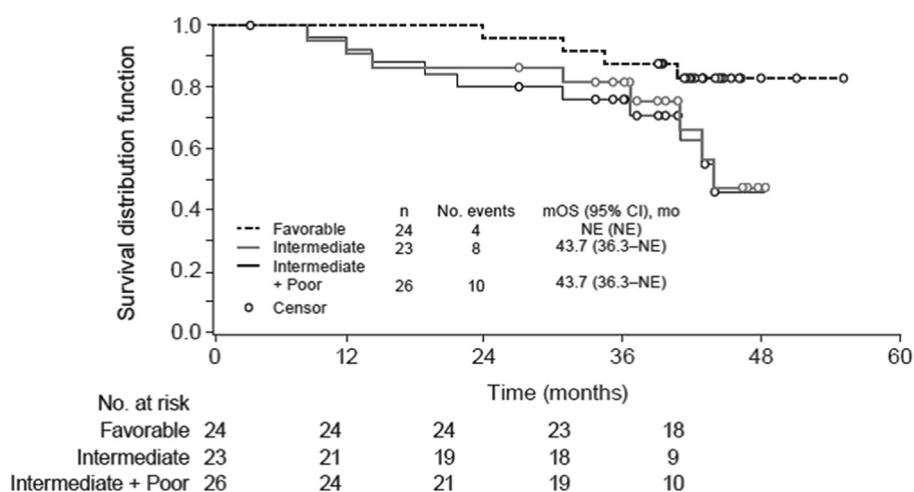
A. Overall population**B. By IMDC group**

Fig. 1. Overall survival by (A) overall population and (B) the IMDC group. IMDC risk group was unknown for two patients. CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mOS, median overall survival; NE, not evaluable; OS, overall survival; PEM, pembrolizumab.

3.3. Safety

Median (range) time on treatment with axitinib plus pembrolizumab ($n = 52$) was 14.5 months (0.03–46.7), median time on pembrolizumab after axitinib discontinuation ($n = 10$) was 9.0 months (1.4–31.8), and median time on axitinib after pembrolizumab discontinuation ($n = 11$) was 7.5 months (2.5–21.8). After stopping study treatment, 22 patients received subsequent systemic therapy, including nivolumab, axitinib or cabozantinib ($n = 6$ each); everolimus or pazopanib ($n = 3$ each); bevacizumab, ipilimumab, cabozantinib S-malate, lenvatinib, or investigational drug ($n = 2$ each); and atezolizumab, pazopanib hydrochloride, or uncoded ($n = 1$ each). Other follow-up therapies included cancer-related radiotherapy ($n = 4$) and surgery ($n = 3$; interventional radiology lung aspiration biopsy,

laparoscopic resection, right hepatic artery radio-embolization). Based on exploratory analyses, of the 38 patients who were still alive, 13 (34.2%) patients received additional systemic therapy, two (5.3%) radiotherapy, and two (5.3%) surgery. Median time to first therapy/surgery was 33.0, 23.7 and 24.5 months in patients who received systemic therapy, radiotherapy and surgery, respectively.

Grade 3/4 AEs were reported in 38 (73.1%) patients (Table 1). The most common AEs reported were diarrhoea (84.6%), fatigue (80.8%), hypertension (53.8%), cough (48.1%) and dysphonia (48.1%) (Table 1). The most common AEs related to treatment with axitinib or pembrolizumab were fatigue (75.0%), diarrhoea (73.1%), hypertension (50.0%) and dysphonia (46.2%) (Table 1). Drug discontinuation and dose reduction due to AEs are shown in Table 1.

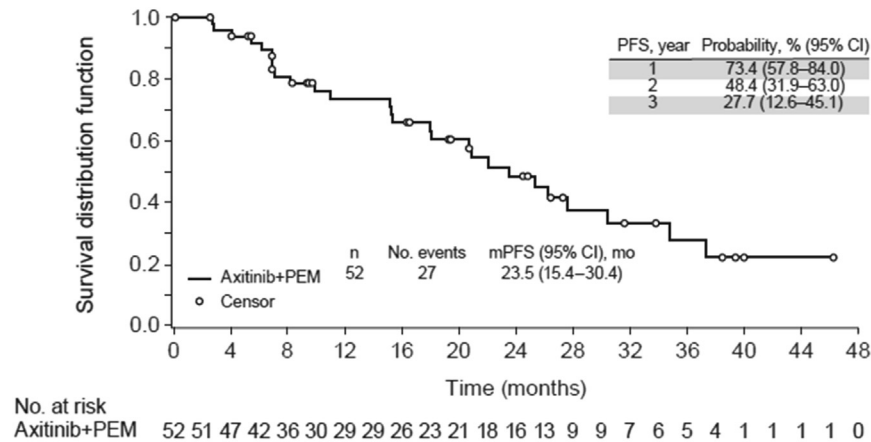
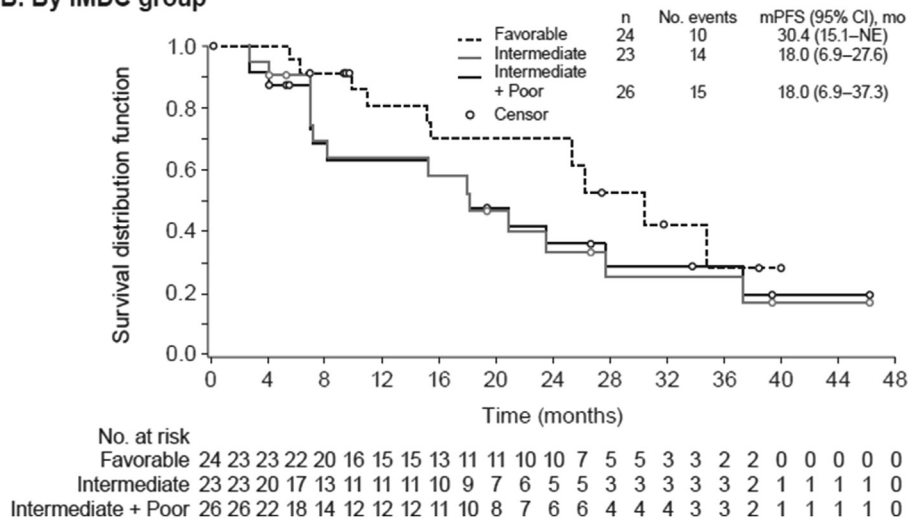
A. Overall population**B. By IMDC group**

Fig. 2. Progression-free survival by (A) overall population and (B) the IMDC group. The IMDC risk group was unknown for two patients. CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mPFS, median progression-free survival; NE, not evaluable; PEM, pembrolizumab; PFS, progression-free survival.

4. Discussion

After ~4 years of follow-up, the clinical benefit with axitinib plus pembrolizumab treatment was maintained, with the majority of patients (73.1%) still alive at the time of the analysis. The median OS was not reached in the overall population nor in patients with IMDC favourable-risk disease and was 43.7 months in patients with intermediate-risk or intermediate/poor-risk disease. The extended medians of PFS (23.5 versus 20.9 months) and DoR (22.1 versus 18.6 months) compared with the primary analysis [10] further demonstrated the durable response to axitinib plus pembrolizumab in patients with advanced RCC.

In the primary analysis of this phase I trial, with a median follow-up of 20.4 months, 38 of 52 (73%) patients achieved objective response, more than 90% of

patients had tumour shrinkage, and only three patients had progressive disease as best response [10]. Of the initial 38 responders, 30 (79%) patients were still alive after ~4 years of follow-up, as well as eight of 14 (57%) patients who were non-responders.

The updated analysis from the phase III trial of axitinib plus pembrolizumab versus sunitinib (KEYNOTE-426), with a median follow-up of 27 months, was recently published [13]. The two-year estimated probability of survival (88% versus 74%) and PFS (48% versus 38%) were higher in the phase I trial of axitinib plus pembrolizumab than in those treated with axitinib plus pembrolizumab in the phase III trial. Similarly, median PFS was longer (23.5 versus 15.4 months) and more patients achieved objective response (73% versus 60%), but median DoR was similar (22.1 versus 23.5 months) in the phase I versus phase III trial [10,13]. Factors

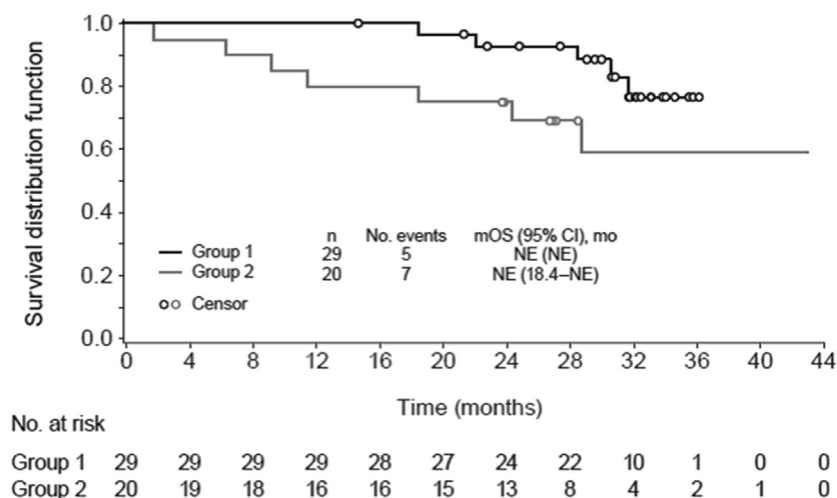
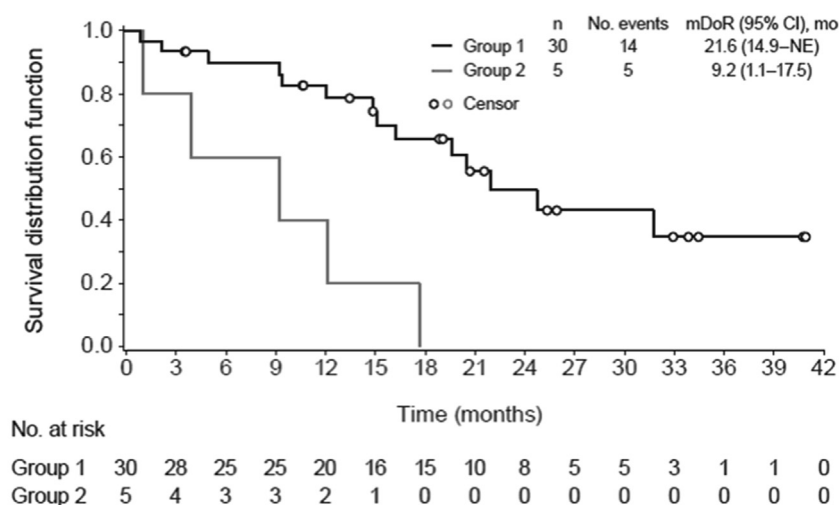
A. Overall survival**B. Duration of response**

Fig. 3. Landmark analysis of (A) overall survival and (B) duration of response by time on axitinib treatment (A) Group 1 = patients still on axitinib treatment at ≥ 1 year. Group 2 = patients not on axitinib treatment at 1 year (B) Group 1 = patients still on axitinib treatment at ≥ 6 months. Group 2 = patients not on axitinib treatment at 6 months. CI, confidence interval; mDoR, median duration of response; mOS, median overall survival; NE, not evaluable.

potentially responsible for these differences include the following ones: 1) all patients in the phase I trial had prior nephrectomy versus 83% in the phase III trial [11] and 2) tumour response was assessed by the investigators in the phase I trial versus blinded, independent central review. In addition, the higher OS rate in the phase I trial is likely due to the higher number of patients with favourable-risk disease (46%) versus the phase III trial (32%) [11] and possibly highlights the impact that IMDC risk-group distributions on the efficacy results from various trials in patients with RCC. Though exploratory in nature, median PFS in the phase I trial was also longer in patients with favourable and intermediate + poor-risk disease, respectively (30.4 and 18.0 months) than that in the phase III trial (20.8 and 12.7 months), suggesting other factors likely account for

the difference between the two studies [13]. Nonetheless, it will be interesting to examine whether the durability of benefit observed in the phase I trial will be seen in patients receiving the axitinib plus pembrolizumab combination in the phase III trial and in clinical practice.

Data from other phase III combination-therapy trials have been recently published. In an updated analysis of the phase III trial of axitinib plus avelumab versus sunitinib (JAVELIN Renal 101), with a median follow-up of 19.3 months, OS benefit was inconclusive, with 27% deaths in both arms of the overall population [14]. Median PFS was 13.3 months, ORR 53%, and median DoR 18.5 months [14]. In the CheckMate 9 ER trial of cabozantinib plus nivolumab versus sunitinib, with a median follow-up of 18 months, median PFS was 16.6 months, ORR 55.7% and OS showed a significant

Table 1

Adverse events with axitinib plus pembrolizumab for the entire study period, safety analysis set.

Adverse events, n (%)		Total N = 52
Any AE		52 (100)
Grade 3–4		38 (73.1)
Discontinued either drug due to AEs		20 (38.5)
Discontinued axitinib due to AEs		17 (32.7)
Discontinued pembrolizumab due to AEs		13 (25.0)
Discontinued both drugs due to AEs		10 (19.2)
Axitinib dose reduction due to AEs		16 (30.8)
Adverse events ($\geq 25\%$) All-causality		Related to axitinib or pembrolizumab
Diarrhoea	44 (84.6)	38 (73.1)
Fatigue	42 (80.8)	39 (75.0)
Hypertension	28 (53.8)	26 (50.0)
Cough	25 (48.1)	8 (15.4)
Dysphonia	25 (48.1)	24 (46.2)
ALT increased	23 (44.2)	20 (38.5)
Decreased appetite	23 (44.2)	19 (36.5)
Hypothyroidism	23 (44.2)	19 (36.5)
Nausea	23 (44.2)	19 (36.5)
AST increased	19 (36.5)	16 (30.8)
Constipation	19 (36.5)	7 (13.5)
PPE syndrome	19 (36.5)	19 (36.5)
Arthralgia	18 (34.6)	12 (23.1)
Proteinuria	18 (34.6)	15 (28.8)
Weight decreased	18 (34.6)	15 (28.8)
Headache	17 (32.7)	12 (23.1)
Vomiting	17 (32.7)	10 (19.2)
Blood creatinine increased	16 (30.8)	9 (17.3)
Dizziness	16 (30.8)	7 (13.5)
Dyspnoea	16 (30.8)	10 (19.2)
Abdominal pain	15 (28.8)	11 (21.2)
Nasal congestion	14 (26.9)	2 (3.8)
Rash	14 (26.9)	9 (17.3)
Oral pain	13 (25.0)	12 (23.1)

Medical Dictionary for Regulatory Activities (version 22.0) coding dictionary applied.

AE, adverse event; ALT, alanine aminotransferase; AST, alanine aminotransferase; PPE, palmar-plantar erythrodysesthesia.

benefit with the combination (HR = 0.60) [15]. In the updated analysis of the phase III CheckMate 214 trial of nivolumab plus ipilimumab versus sunitinib, with a median follow-up of 43.6 months for the nivolumab plus ipilimumab arm, median OS was not reached and the probability of survival at 42 months was 56% in the intent-to-treat population [16]. Median PFS was 12.4 months, ORR 39% and DoR not reached [16].

As stated earlier, the differences in outcomes between these trials and the axitinib plus pembrolizumab combination trials could be attributed to the differences in IMDC risk-group distribution of the patient population, as well as differences in trial design and time and location of trial conduct. Specifically, the number of patients with IMDC favourable risk in JAVELIN Renal 101 (21%), CheckMate 9 ER (23%), CheckMate 214 (23%), KEYNOTE-426 (32%), and phase I axitinib plus pembrolizumab (46%) differed, and this fact, together with

the availability of subsequent treatment options, makes it hazardous to compare results between trials even for the phase III trials that used a common control arm. Nevertheless, all studies showed that combination therapy as first-line treatment for RCC may be preferable to a single-agent VEGF-receptor tyrosine kinase inhibitor (e.g. sunitinib) for many, if not most patients.

During this long period of follow-up, there were no new safety signals, and no new cumulative AEs or new AEs. AEs were tolerable and clinically manageable with standard-of-care treatments and dose interruptions and/or reductions. Fatigue (75%), diarrhoea (73%), hypertension (50%), and dysphonia (46%) were among the most common treatment-related AEs reported with axitinib plus pembrolizumab. These are similar to the most common AEs reported with first-line axitinib monotherapy, which includes diarrhoea (50.0%), hypertension (49.0%), weight decrease (37%), and fatigue (33%) [6]. Fatigue (13%) and diarrhoea (12%) were also most commonly reported with pembrolizumab monotherapy, together with pruritus (18%) and hypothyroidism (13%) [2].

Although updated efficacy data looked promising, outcomes could have been better if we did not censor patients who stopped treatment because of toxicity even if they were ongoing responders ($n = 10$ in the current study) [10]. This censoring approach in the study design also prevented the ability to identify ‘treatment-free survival,’ an endpoint that is increasingly examined in the context of immunotherapy trials as a measure of the durable effect of immunotherapy [17]. The median duration of treatment with axitinib plus pembrolizumab (14.5 months), which resulted in longer median PFS and median DoR (23.5 and 22.1 months, respectively), may suggest that a number of patients had responses that were maintained off treatment. Interestingly, patients who were still on axitinib either alone or in combination with pembrolizumab for ≥ 1 year and ≥ 6 months, respectively, had longer OS and DoR compared with patients who stopped treatment or received pembrolizumab monotherapy. Long-term data from the KEYNOTE-426 trial will provide additional insights into the durability of tumour responses to axitinib plus pembrolizumab and whether or not the responses are maintained if axitinib, pembrolizumab, or both treatments are discontinued.

In conclusion, after ~4 years of follow-up, the combination of axitinib plus pembrolizumab continued to demonstrate substantial clinical benefit in patients with advanced RCC. Most (73.1%) patients remained alive, and there were no new safety signals. The long-term results from this phase I study further support the use of the axitinib plus pembrolizumab combination for first-line treatment of patients with advanced RCC.

Source of support

This study was sponsored by Pfizer in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA.

Ethics approval and consent to participate

This study was conducted in compliance with the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. All patients provided written informed consent.

Consent for publication

Not required.

Availability of data and material

Upon request, and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or Europe or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data from Pfizer trials may be requested 24 months after study completion. The de-identified participant data will be made available via a secure portal to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply. To gain access, data requestors must enter into a data access agreement with Pfizer.

Role of the funding source

The study was funded and conducted by Pfizer. The sponsor played a role in the design and conduct of the study; data collection, and analysis, and interpretation of data; and review and approval of the manuscript. Medical writing support was funded by Pfizer.

Authors' contributions

All authors had full access to all data in the trial and take responsibility for the integrity of the data and the accuracy of the data analysis. Michael B Atkins, Toni K Choueiri, Jamal C Tarazi, Kathrine C Fernandez, Mahgull Thakur, and Igor Puzanov contributed to the conceptualisation and design of the trial. Michael B

Atkins, Elizabeth R Plimack, Igor Puzanov, Mayer N Fishman, David F McDermott, Daniel C Cho, Ulka Vaishampayan, Saby George, Jamal C Tarazi, Kathrine C Fernandez, Rodolfo Perini, Mahgull Thakur, and Toni K Choueiri were responsible for collection and assembly of data. William Duggan completed the statistical analyses. All authors participated in writing the paper and approved the final version of the paper.

Conflict of interest statement

MB Atkins reports institutional research support from Bristol-Myers Squibb, Merck, Pfizer, and Genentech; consulting fees from Pfizer, Novartis, Genentech-Roche, Merck, Exelixis, Eisai, Boehringer Ingelheim, Aveo, Array, Idera, Aduro, Immunocore, Iovance, NewLink, Pharma, Surface, Alexion, Acceleron, COTA, Amgen, Up-to-Date, and AstraZeneca; roles in advisory boards for Bristol-Myers Squibb, Merck, Novartis, Arrowhead, Pfizer, Glactone, Werewolf, Fathom, Pneuma, Leads Pharma, Pyxis; and stock option in Werewolf and Pyxis.

ER Plimack reports consulting fees from and/or served roles in advisory boards for Bristol-Myers Squibb, Exelixis, Genentech, Incyte, Janssen, Merck, AstraZeneca, and Pfizer; and grant or clinical trial support from Astellas, AstraZeneca, Bristol-Myers Squibb, Genentech, Merck, Peloton, and Pfizer.

I Puzanov reports consulting fees from and/or served on advisory boards for Amgen, Roche, and AbbVie and clinical trial support through his institution from Merck, Amgen, Roche, Nektar, Idera, and Bristol-Myers Squibb.

MN Fishman reports research funding from Bristol-Myers Squibb, Exelixis, Eisai, Genentech, Acceleron, Merck, Prometheus / Clinigen, Nektar, Alkermes, and Pfizer; and speakers bureau roles for Astellas, Bristol-Myers Squibb, Exelixis, EMD Serono, Pfizer; and paid roles in advisory boards for Alkermes, Clinigen, Eisai, Merck, Pfizer, Seattle Genetics.

DF McDermott reports consulting fees from Bristol-Myers Squibb, Pfizer, Novartis, Genentech-Roche, Merck, Eisai, Array BioPharma, Prometheus, and Exelixis.

DC Cho reports consulting fees from Pfizer, Genentech, Prometheus, Bristol-Myers Squibb, PureTech Health, Torque Pharmaceuticals, and Exelixis.

U Vaishampayan reports research support from Astellas, Bristol-Myers Squibb, and Exelixis and consulting fees from Exelixis, Merck, Alkermes, Pfizer, Pfizer, Bayer, and Bristol-Myers Squibb.

S George reports consulting fees from and advisory roles for Pfizer, Exelixis, Bristol-Myers Squibb, Sanofi/Genzyme, Genentech, Bayer, Corvus, EMD Serono, Seattle Genetics/Astellas, Eisai, and Merck and institutional grant support from Bristol-Myers Squibb,

Novartis, Bayer, Pfizer, Merck, Seattle Genetics/Astellas, Eisai, Calithera Biosciences, Immunomedics, Corvus Pharmaceuticals, and Agensys.

JC Tarazi, W Duggan, M Thakur, and KC Fernandez reports being employees of Pfizer and stock or stock options in Pfizer.

R Perini reports an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TK Choueiri reports research support (institutional and personal) from AstraZeneca, Alexion, Bayer, Bristol-Myers Squibb/E.R. Squibb & Sons LLC, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Ipsen, TRACON, Genentech, Roche, Roche Products Ltd, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Prometheus, Corvus, Calithera, Analysis Group, Sanofi/Aventis, Takeda, National Cancer Institute (NCI), National Institutes of Health (NIH), and Department of Defense (DOD); honoraria from AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol-Myers Squibb/E.R. Squibb & Sons LLC, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Genentech, Roche, Roche Products Ltd, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus, Corvus, Ipsen, Up-to-Date, Analysis Group, National Comprehensive Cancer Network (NCCN), Michael J. Hennessy (MJH) Associates Inc, Research to Practice, Lpath, *Kidney Cancer* journal, Clinical Care Options, PlatformQ, Navinata Health, Harborside Press, American Society of Medical Oncology, *New England Journal of Medicine*, *Lancet Oncology*, Heron Therapeutics, Lilly, American Society of Clinical Oncology (ASCO), and European Society of Medical Oncology (ESMO); provided consultancy or advisory services to AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol-Myers Squibb/E.R. Squibb & Sons LLC, Cerulean, Eisai, Foundation Medicine Inc, Exelixis, Genentech, Heron Therapeutics, Lilly, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus, Corvus, Ipsen, Up-to-Date, NCCB, Analysis Group, Pionyr, and Tempest; stock ownership in Pionyr and Tempest; contributions toward International Patent Application No. PCT/US2018/12,209, entitled “PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response,” filed January 3, 2018, claiming priority to U.S. Provisional Patent Application No. 62/445,094, filed January 11, 2017, and International Patent Application No. PCT/US2018/058,430, entitled “Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy,” filed October 31, 2018, claiming priority to U.S. Provisional Patent Application No. 62/581,175, filed November 3, 2017; and travel, accommodations, and expenses in relation to consulting, advisory roles, and/or honoraria.

Acknowledgements

The authors would like to acknowledge the contributions to the study of David Mauro and Steve Keefe of Merck & Co., Inc., Kenilworth, NJ, USA. They thank the patients who participated in this study and their families. Medical writing support was provided by Vardit Dror, PhD, of Engage Scientific Solutions, and was funded by Pfizer.

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