Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial

Michael B Atkins, Elizabeth R Plimack, Igor Puzanov, Mayer N Fishman, David F McDermott, Daniel C Cho, Ulka Vaishampayan, Saby George, Thomas E Olencki, Jamal C Tarazi, Brad Rosbrook, Kathrine C Fernandez, Mariajose Lechuga, Toni K Choueiri

Summary

Background Previous studies combining PD-1 checkpoint inhibitors with tyrosine kinase inhibitors of the VEGF pathway have been characterised by excess toxicity, precluding further development. We hypothesised that axitinib, a more selective VEGF inhibitor than others previously tested, could be combined safely with pembrolizumab (anti-PD-1) and yield antitumour activity in patients with treatment-naive advanced renal cell carcinoma.

Methods In this ongoing, open-label, phase 1b study, which was done at ten centres in the USA, we enrolled patients aged 18 years or older who had advanced renal cell carcinoma (predominantly clear cell subtype) with their primary tumour resected, and at least one measureable lesion, Eastern Cooperative Oncology Group performance status 0–1, controlled hypertension, and no previous systemic therapy for renal cell carcinoma. Eligible patients received axitinib plus pembrolizumab in a dose-finding phase to estimate the maximum tolerated dose, and additional patients were enrolled into a dose-expansion phase to further establish safety and determine preliminary efficacy. Axitinib 5 mg was administered orally twice per day with pembrolizumab 2 mg/kg given intravenously every 3 weeks. We assessed safety in all patients who received at least one dose of axitinib or pembrolizumab; antitumour activity was assessed in all patients who received study treatment and had an adequate baseline tumour assessment. The primary endpoint was investigator-assessed dose-limiting toxicity during the first two cycles (6 weeks) to estimate the maximum tolerated dose and recommended phase 2 dose. This study is registered with ClinicalTrials.gov, number NCT02133742.

Findings Between Sept 23, 2014, and March 25, 2015, we enrolled 11 patients with previously untreated advanced renal cell carcinoma to the dose-finding phase and between June 3, 2015, and Oct 13, 2015, we enrolled 41 patients to the dose-expansion phase. All 52 patients were analysed together. No unexpected toxicities were observed. Three dose-limiting toxicities were reported in the 11 patients treated during the 6-week observation period (dose-finding phase): one patient had a transient ischaemic attack and two patients were only able to complete less than 75% of the planned axitinib dose because of treatment-related toxicity. At the data cutoff date (March 31, 2017), 25 (48%) patients were still receiving study treatment. Grade 3 or worse treatment-related adverse events occurred in 34 (65%) patients; the most common included hypertension (n=12 [23%]), diarrhoea (n=5 [10%]), fatigue (n=5 [10%]), and increased alanine aminotransferase concentration (n=4 [8%]). The most common potentially immune-related adverse events (probably related to pembrolizumab) included diarrhoea (n=15 [29%]), increased alanine aminotransferase concentration (n=9 [17%]) or aspartate aminotransferase concentration (n=7 [13%]), hypothyroidism (n=7 [13%]), and fatigue (n=6 [12%]). 28 (54%) patients had treatment-related serious adverse events. At data cutoff, 38 (73%; 95% CI 59·0–84·4) patients achieved an objective response (complete or partial response).

Interpretation The treatment combination of axitinib plus pembrolizumab is tolerable and shows promising antitumour activity in patients with treatment-naive advanced renal cell carcinoma. Whether or not the combination works better than a sequence of VEGF pathway inhibition followed by an anti-PD-1 therapy awaits the completion of a phase 3 trial comparing axitinib plus pembrolizumab with sunitinib monotherapy (NCT02853331).

Funding Pfizer Inc.

Lancet Oncol 2018

Published Online
February 10, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30081-0

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(18)30092-5

Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA (Prof M B Atkins MD); **Fox Chase Cancer Center, Philadelphia, PA, USA** (E R Plimack MD); **Vanderbilt University Medical Center, Nashville, TN, USA** (Prof I Puzanov MD); **Roswell Park Cancer Institute, Buffalo, NY, USA** (Prof I Puzanov, S George MD); **Moffitt Cancer Center, Tampa, FL, USA** (Prof M N Fishman MD); **Beth Israel Deaconess Medical Center, Boston, MA, USA** (Prof D F McDermott MD); **New York University Langone Medical Center, New York, NY, USA** (D C Cho MD); **Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA** (Prof U Vaishampayan MD); **Ohio State University Wexner Medical Center, Columbus, OH, USA** (T E Olencki DO); **Pfizer Oncology, San Diego, CA, USA** (J C Tarazi MD, B Rosbrook MS); **Pfizer Oncology, Cambridge, MA, USA** (K C Fernandez MD); **Pfizer SrL, Milan, Italy** (M Lechuga MD); **and Dana-Farber Cancer Institute, Boston, MA, USA** (T K Choueiri MD)

Correspondence to:
Prof Michael B Atkins, Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC 20007, USA
mba41@georgetown.edu

Introduction

Targeted therapy with VEGFR inhibitors has substantially improved outcomes for patients with advanced renal cell carcinoma over the past decade. However, most patients treated with VEGFR inhibitors eventually develop drug resistance and exhibit disease progression while on therapy.[1,2] Consequently, novel therapeutic approaches are needed to circumvent drug resistance and provide a more durable therapeutic response.

Novel immunotherapies target the immune checkpoint pathway mediated by the PD-1 receptor and its ligands, PD-L1 and PD-L2. Binding of PD-1 receptor to its ligands dampens the antitumour immune response, thus allowing tumours to survive and proliferate. Upregulation of PD-1 receptor on tumour-infiltrating lymphocytes, and its ligand PD-L1 on the surface of tumour cells, are associated with more aggressive disease and poor prognosis.[3–5] Drugs that block the binding of PD-1

Research in context

Evidence before this study

Despite substantial improvements over the past decade in outcomes for patients with advanced renal cell carcinoma with VEGF pathway inhibitors, durable and complete responses in these patients have been rarely achieved. The standard first-line drugs sunitinib and pazopanib lead to a median progression-free survival of around 8–12 months. Drugs that block the binding of PD-1 receptor to its ligands can produce durable responses in a few patients with advanced renal cell carcinoma whose disease has progressed following VEGF pathway-inhibitor therapy. However, previous efforts to combine sunitinib or pazopanib with an anti-PD-1 antibody, aimed at prolonging progression-free survival and response durations, were curtailed due to excessive toxicity. A formal systematic review was not done before doing this trial because most of the work combining VEGF pathway inhibitors with checkpoint inhibitors is new and not yet published. In an effort to develop a tolerable and therefore more effective combination regimen involving an anti-VEGF drug and an anti-PD-1 antibody, we did an open-label, phase 1b trial combining axitinib, a more specific and selective VEGF pathway inhibitor, with the anti-PD-1 antibody pembrolizumab in patients with treatment-naive metastatic renal cell carcinoma.

Added value of this study

This study showed the combination of axitinib and pembrolizumab is tolerable in patients with treatment-naive advanced renal cell carcinoma. This outcome contrasts with the toxicities reported in other clinical trials that combined checkpoint inhibitors with other tyrosine kinase inhibitors of the VEGF pathway. The proportion of patients who achieved an objective response was 73% and median progression-free survival exceeded 20 months. This antitumour activity is superior to that expected and that has been reported from axitinib or PD-1 pathway-inhibitor monotherapy alone.

Implications of all the available evidence

On the basis of the results of this phase 1b trial, the US Food and Drug Administration granted the axitinib–pembrolizumab combination a breakthrough status. A randomised phase 3 trial (NCT0285331) comparing the combination to sunitinib monotherapy is underway, and if this trial confirms the results for the combination reported here, it is likely to lead to a new first-line treatment option for patients with advanced renal cell carcinoma.

receptor to its ligands can produce durable responses in a subset of patients with advanced renal cell carcinoma,[6,7] and have shown efficacy in patients whose disease has progressed following VEGF pathway inhibitor therapy.[8,9]

Results from animal studies show that angiogenesis inhibition can enhance the antitumour activity of immunotherapies by increasing T-cell infiltration into tumours.[10] Furthermore, mouse models show that simultaneous inhibition of the VEGF and PD-1 pathways increased T-cell infiltration into tumours in a synergistic manner.[11] Clinical studies[12,13] combining tyrosine kinase inhibitors (TKIs) of the VEGF pathway with PD-1 checkpoint inhibitors have shown clinical benefit in patients with metastatic renal cell carcinoma, but several of these combinations have not been feasible due to unacceptable toxicity. Many of these toxicities were related to off-target effects of these multitargeted TKIs, suggesting that a more selective inhibitor of the VEGF pathway might be better tolerated than these multitargeted drugs in combination with an anti-PD-1 drug and produce synergistic antitumour activity. Preliminary results from a phase 1b trial[14] of axitinib—a potent, selective inhibitor of VEGFR 1–3—in combination with the anti-PD-L1 drug avelumab showed antitumour activity and a manageable safety profile in patients with previously untreated advanced renal cell carcinoma.

See Online for appendix

Axitinib, which is approved for the second-line treatment of patients with advanced renal cell carcinoma, has shown clinical activity and an acceptable safety profile as a monotherapy in the first-line setting.[15,16] Median progression-free survival with first-line axitinib in patients with metastatic renal cell carcinoma was 14·6 months (95% CI 11·5–17·5) in a phase 2 study[15] and 10·1 months (7·2–12·1) in a randomised controlled phase 3 trial,[16] but these outcomes were not significantly superior to those achieved with sorafenib. Pembrolizumab is a humanised monoclonal antibody that blocks PD-1 and PD-L1 interaction, which enhances and prolongs immune response to the tumour microenvironment.[17,18] We postulated that the combination of axitinib with pembrolizumab might be well tolerated and provide improved clinical benefit in patients with previously untreated advanced renal cell carcinoma versus that seen with either treatment alone.

This ongoing open-label phase 1b, multicentre study evaluated the safety and efficacy of axitinib in combination with pembrolizumab in patients with treatment-naive advanced renal cell carcinoma. The study consisted of two phases: a dose-finding phase to estimate the maximum tolerated dose and select a recommended phase 2 dose, and a dose-expansion phase. We report safety and activity results from both phases of this study.

Methods

Study design and participants

This open-label, phase 1b trial was done at ten centres in the USA (appendix p 1). Eligible patients were aged 18 years or older with histologically or cytologically confirmed advanced renal cell carcinoma, predominantly clear cell subtype, who had undergone resection of their

primary tumour; with at least one measurable lesion, defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; controlled hypertension (baseline blood pressure ≤150/90 mm Hg); and adequate bone marrow, renal, and liver function (appendix pp 41–42). Patients enrolled also had to provide an archival tumour biospecimen and undergo a baseline de-novo biopsy from a metastatic lesion. We excluded patients if they had previous systemic therapy for metastatic renal cell carcinoma; disease progression or relapse within 12 months after completing adjuvant or neoadjuvant treatment; or previous treatment with axitinib, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 antibody (appendix pp 42–45). Additionally, we excluded patients if they had a diagnosis of immunodeficiency, active or documented history of autoimmune disease, gastrointestinal abnormalities, active or documented history of bleeding disorder, or a history of known active seizure disorder (appendix p 43).

The study protocol (appendix pp 6–114), amendments, and informed consent forms were reviewed and approved by the institutional review board or independent ethics committee at each study centre. The study was done in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Declaration of Helsinki, and applicable local regulatory requirements and laws. All patients provided written informed consent before study initiation.

Procedures

Axitinib was administered orally (starting dose 5 mg twice daily) beginning on day –7 (ie, 7 days before the start of cycle 1), and pembrolizumab 2 mg/kg intravenously on day 1 of each 3-week cycle. The possible dose-finding scenarios based on the starting dose level tolerability were: dose level 1, axitinib 5 mg twice daily plus pembrolizumab 2 mg/kg on day 1 of each 3-week cycle and dose level –1, axitinib 3 mg twice daily plus pembrolizumab 2 mg/kg on day 1 of each 3-week cycle. Dose level –1 was to be explored only if the maximum tolerated dose was exceeded at dose level 1. No intra-patient dose escalation was permitted during the dose-finding phase. Planned treatment duration with pembrolizumab was 2 years based on its use in other studies,[19] calculated from the first dose of pembrolizumab. After completing treatment with pembrolizumab, patients who achieved an objective response or stable disease were able to continue treatment with single-drug axitinib until confirmed disease progression, patient refusal, or unacceptable toxicity, whichever occurred first. Per the protocol and according to the investigator's judgment, if patients with evidence of disease progression were still deriving clinical benefit, they were eligible for continued treatment. Retreatment with pembrolizumab for patients who discontinued treatment because they attained a confirmed complete response and then had radiological disease progression was allowed. No planned breaks of axitinib treatment or alternative axitinib treatment schedules were used in this study. Treatment with axitinib was paused as necessary in the case of toxicity and then resumed at the dose indicated by the protocol when the toxicity was resolved.

The expansion-phase dose was the recommended phase 2 dose. During the dose-finding phase, the study design did not allow testing doses higher than the recommended dose of axitinib 5 mg twice daily and pembrolizumab 2 mg/kg. In the expansion phase, intra-patient dose escalation of axitinib was permitted after 12 weeks of treatment based on tolerability and axitinib prescribing information.[20] Patients who tolerated the starting dose with no grade 2 or worse drug-related adverse events had the option to have their axitinib dose increased from 5 mg twice daily to 7 mg twice daily, and then to a maximum of 10 mg twice daily (unless their blood pressure was >150/90 mm Hg or the patient was receiving antihypertensive medication).

Tumours were assessed, using RECIST version 1.1 (appendix p 108), at baseline (screening), week 12, and every 6 weeks thereafter. After 66 weeks from study initiation, tumours were assessed every 12 weeks. Tumour responses had to be confirmed with a repeat scan at least 4 weeks later. Radiological tumour assessments were done whenever disease progression was suspected (eg, symptomatic deterioration) and at time of withdrawal from treatment (if not done in the previous 6 weeks). If disease progression was suspected, tumour assessment was repeated again at least 4 weeks later to confirm this assessment. Brain scans (CT or MRI) were done at baseline or when metastasis was suspected. Bone scan (bone scintigraphy) or ^{18}F-fluorodeoxyglucose PET (^{18}F-FDG-PET) or CT was required at baseline and, if bone metastases were present at baseline, every 12 weeks thereafter. Otherwise, bone imaging was required only if new metastases were suspected.

We assessed adverse events throughout the study for their incidence, severity (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03), seriousness (see definitions on appendix p 82), and relatedness to investigational treatment. We analysed blood chemistry, haematology, coagulation, and urinalysis at baseline and after every treatment cycle (ie, every 3 weeks). We recommended that blood chemistry tests for liver functions be done weekly for the first three treatment cycles. We monitored thyroid functions at baseline, then every other cycle. All assessments were repeated when clinically indicated. We assessed vital signs and verification of concurrent medications at each clinic visit; physical examination and 12-lead electrocardiogram were assessed at screening, day 1 of cycle 1, and at the end of treatment (appendix pp 74–75).

We used paraffin-embedded tumour tissue blocks obtained from tumour biopsy specimens or archival

	All participants (n=52)
Age (years)	
Mean	61·2 (9·2)
Median	63·0 (57·0–67·5)
<65 years	29 (56%)
≥65 years	23 (44%)
Sex	
Male	41 (79%)
Female	11 (21%)
Race	
White	45 (87%)
Black	1 (2%)
Asian	4 (8%)
Other	2 (4%)
ECOG performance status	
0	39 (75%)
1	10 (19%)
Not reported	3 (6%)
IMDC criteria risk group	
Favourable	24 (46%)
Intermediate	23 (44%)
Poor	3 (6%)
Unknown	2 (4%)
Fuhrman grade	
1	2 (4%)
2	12 (23%)
3	18 (35%)
4	14 (27%)
Not done	6 (12%)
Histology	
Clear cell renal cell carcinoma	52 (100%)
Sarcomatoid features	1 (2%)
Sites of metastasis	
Lung	30 (58%)
Liver	7 (14%)
Adrenal	7 (14%)
Pancreas	5 (10%)
Lymph nodes	26 (50%)
Other	22 (42%)
Time since initial pathological diagnosis	
Patients (n)	46
Median (months)	20·3 (7·4–65·4)
Unspecified (n)	6

Data are n (%), mean (SD), median (IQR), or as specified. ECOG=Eastern Cooperative Oncology Group. IMDC=International Metastatic Database Consortium.

Table 1: **Patient demographics and baseline characteristics**

tumour tissue of patients enrolled in the study with informed consent for biomarker analyses. Immunohistochemistry analyses were done under Good Clinical Laboratory Practice conditions (Quintiles, Edinburgh, UK). The PD-L1 (mouse monoclonal 22C3; Dako Inc, Agilent Technologies, Santa Clara, CA, USA) immunohistochemistry assay was designed and validated as a fit-for-purpose laboratory-developed test. We did the analyses to categorise the tumour specimens as negative or positive based on the following: PD-L1 negative if the tumour proportion score (the percentage of viable tumour cells showing partial or complete membrane staining at any intensity) was lower than 1% versus PD-L1 positive if the tumour proportion score was 1% or higher.[21] This cutoff was selected a priori. Assessment of other biomarkers including tumour VEGF-A will be reported in a separate publication.

Outcomes

The primary endpoint was investigator-assessed dose-limiting toxicity during the first two treatment cycles (6 weeks) of the dose-finding phase to estimate the maximum tolerated dose and recommended phase 2 dose. Dose-limiting toxicity was classified as any of the following: grade 4 neutropenia or thrombocytopenia, grade 3 or worse neutropenic infection or thrombocytopenia with bleeding, or febrile neutropenia; non-haematological grade 3 or worse toxicity; and inability to complete at least 75% of axitinib dosing or two infusions of pembrolizumab due to treatment-related toxicity occurring during the 6-week observation period for dose-limiting toxicities and attributable to one or both study drugs.

Secondary endpoints were adverse events, laboratory abnormalities, vital signs, PD-L1 biomarker status, pharmacokinetics, immunogenicity (anti-drug antibodies), serum and whole blood biomarkers, and antitumour activity. Antitumour activity was assessed as the proportion of patients who achieved an objective response, defined as those who achieved a confirmed complete response or confirmed partial response according to RECIST version 1.1 definitions (≥30% decrease in tumour size from baseline), and as duration of response (defined as the time from the first documentation of objective tumour response [complete or partial response] that was subsequently confirmed until the first documentation of objective tumour progression or death due to any cause, whichever occurred first), progression-free survival (defined as time from first pembrolizumab dose to first documentation of objective tumour progression, or on-study death due to any cause, whichever occurred first), and overall survival (defined as the time from the first dose of study treatment to the date of death due to any cause). Patients who were taken off treatment because of toxicity, without evidence of disease progression, had their progression-free survival censored at the time of their last on-study CT scan assessment.

Statistical analyses

We estimated that up to 20 dose-limiting toxicity evaluable patients would need to be enrolled in the dose-finding phase to enable us to obtain a reliable and accurate estimate of the maximum tolerated dose. Further inclusion of 40 patients in the dose-expansion phase

would allow achievement of an event of interest with a standard error (SE) of 0·08 or lower. The de-escalation rules in the dose-finding phase followed the modified toxicity probability interval method.[22] Maximum tolerated dose estimate was the highest dose of axitinib and pembrolizumab associated with the occurrence of dose-limiting toxicities in fewer than 33% of patients.

We summarised safety data descriptively and included all enrolled patients who received at least one dose of axitinib or pembrolizumab. We considered all patients who received study treatment (from the two phases of the trial) and had an adequate baseline tumour assessment as evaluable for antitumour activity using standard RECIST version 1.1 criteria. Patient responses were regarded as indeterminate if they had stable disease or partial response not confirmed with a follow-up scan, or no follow-up scans available. We summarised the proportion of patients who achieved an objective response using percentages and two-sided exact 95% CIs. We analysed time to response, duration of tumour response, progression-free survival, and overall survival using the Kaplan-Meier method, and calculated two-sided 95% CIs. According to US Food and Drug Administration (FDA) guidance and as was prespecified in the protocol, we censored progression-free survival data on the date of the last evaluable tumour assessment documenting absence of progressive disease for patients who had documentation of disease progression or death after two or more consecutive missed scheduled tumour assessment dates. Therefore, if a death occurred more than 12 weeks after the final tumour assessment, the patient's response was censored at the date of last assessment. We did statistical analyses using SAS version 9.4. This study is registered with ClinicalTrials.gov, number NCT02133742.

Role of the funding source

The study sponsor was involved in study design, data collection, data analyses, and writing of the report. All authors had full access to all data and approved the final content of this report. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Sept 23, 2014, and March 25, 2015, we enrolled 11 patients with previously untreated advanced renal cell carcinoma in the dose-finding phase. Between June 3, 2015, and Oct 13, 2015, we enrolled 41 patients with previously untreated advanced renal cell carcinoma in the dose-expansion phase. Because all 52 patients received the same dose and schedule, they were analysed together (table 1, figure 1). As of March 31, 2017, the data cutoff date, 25 (48%) patients were still on treatment; of these, 22 (88%) were receiving axitinib and pembrolizumab, and three (12%) were receiving pembrolizumab only. Eight (15%) patients had confirmed disease progression but were still receiving treatment. 27 (52%) patients discontinued both study treatments (figure 1). The most common reason for discontinuing both study treatments were adverse events (n=10) and disease progression (n=9), and others were mixed adverse events and disease progression (n=5), global deterioration (n=1), protocol violation (n=1), and because of investigator discretion (n=1). 30 (58%) patients discontinued axitinib because of adverse events (n=16), disease progression (n=9), investigator discretion (n=2), global deterioration of health status (n=1), protocol violation (n=1), and because the patient refused continued treatment for a reason other than an adverse event (n=1). 27 (52%) patients discontinued pembrolizumab early because of adverse events (n=12), disease progression (n=12), and global deterioration of health status (n=1), protocol violation (n=1), and because of investigator discretion (n=1). No patient in this study stopped pembrolizumab because of complete response and then was retreated with it because of subsequent disease progression.

Of the 11 patients treated during the dose-finding phase, three dose-limiting toxicities were reported during the 6-week observation period: one patient had transient ischaemic attack and two patients were unable to complete at least 75% of the planned axitinib dose due to treatment-related toxicity (one due to

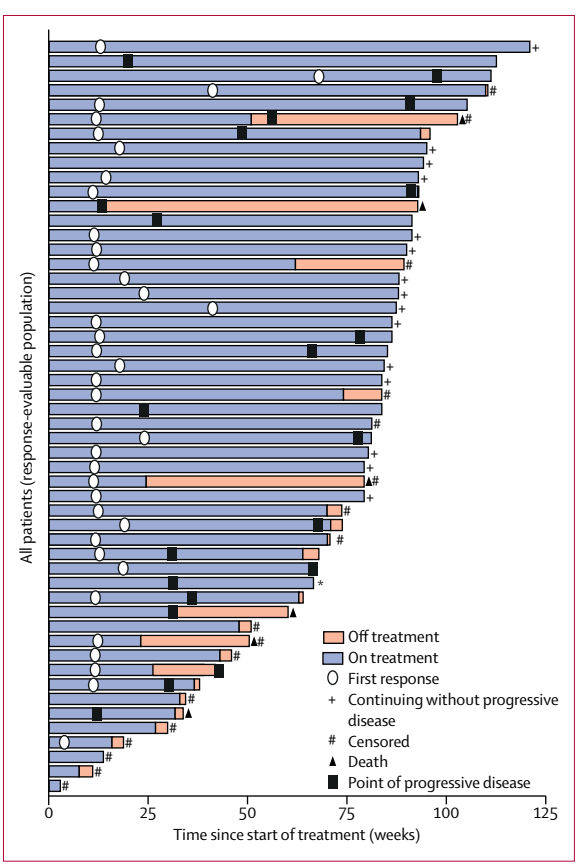

Figure 1: **Tumour swimmer plot for the response-evaluable population (n=52)**
*Patient discontinued but had no off-treatment scan.

	Grade 1–2	Grade 3
Any adverse event	18 (35%)	33 (63%)*
Fatigue	33 (63%)	5 (10%)
Diarrhoea	32 (62%)	5 (10%)
Hypertension	14 (27%)	12 (23%)
Dysphonia	24 (46%)	0
Increased alanine aminotransferase concentration	15 (29%)	4 (8%)
Decreased appetite	18 (35%)	1 (2%)
Hypothyroidism	19 (37%)	0
Nausea	18 (35%)	1 (2%)
Palmar-plantar erythrodysaesthesia	17 (33%)	2 (4%)
Increased aspartate aminotransferase concentration	14 (27%)	2 (4%)
Weight decreased	12 (23%)	2 (4%)
Proteinuria	12 (23%)	1 (2%)
Arthralgia	12 (23%)	0
Dysgeusia	12 (23%)	0
Abdominal pain	11 (21%)	0
Oral pain	10 (19%)	1 (2%)
Dry skin	10 (19%)	0
Dyspnoea	10 (19%)	0
Headache	8 (15%)	2 (4%)
Vomiting	9 (17%)	1 (2%)
Oedema peripheral	9 (17%)	0
Blood creatinine concentration increased	8 (15%)	0
Cough	8 (15%)	0
Dry mouth	8 (15%)	0
Hyperthyroidism	8 (15%)	0
Pruritus	8 (15%)	0
Dizziness	6 (12%)	1 (2%)
Dyspepsia	7 (13%)	0
Oropharyngeal pain	7 (13%)	0
Paraesthesia	7 (13%)	0
Rash	7 (13%)	0
Stomatitis	7 (13%)	0
Anaemia	6 (12%)	0
Constipation	6 (12%)	0
Myalgia	6 (12%)	0
Platelet count decreased	6 (12%)	0

Data are n (%) of all 52 participants. The table lists maximum grade adverse events reported at grades 1–2 in at least 10% patients and grade 3 events.
*One (2%) patient had a grade 4 hyperuricaemia event. No grade 5 treatment-related adverse events were reported.

Table 2: **Adverse events related to axitinib or pembrolizumab treatment in all patients (n=52)**

grade 2–3 headache and the other due to grade 2 headache, fatigue, asthenia, and dehydration). The transient ischaemic attack was deemed possibly related to axitinib, so the axitinib dose was held and then reduced to 3 mg; this patient was still on the reduced dose treatment at the cutoff date. The maximum tolerated dose of this regimen was estimated to be axitinib 5 mg twice per day plus pembrolizumab 2 mg/kg every 3 weeks, which constituted full doses of each agent.

Median duration of axitinib and pembrolizumab treatment was 14·5 months (IQR 5·8–20·2) for all 52 participants. Median duration of pembrolizumab treatment after axitinib discontinuation due to toxicity was 11·1 months (2·8–13·4), and median duration of axitinib treatment after pembrolizumab discontinuation due to toxicity was 11·5 months (2·5–20·4). 32 (62%) patients had their axitinib dose reduced (ie, to <5 mg twice per day for two consecutive doses) because of axitinib-related toxicities and one (2%) patient had the axitinib dose increased to 7 mg twice per day. Overall, patients received almost the full protocol-planned doses of both drugs (median dose of axitinib 8·8 mg/day [IQR 6·6–9·9] and median dose of pembrolizumab 2 mg/kg [1·9–2·0] per cycle; appendix p 2).

Grade 3–4 treatment-related adverse events (related to either axitinib or pembrolizumab, or both) occurred in 34 (65%) patients (table 2); treatment-emergent adverse events (of any cause) are shown in the appendix (p 3). The most common grade 3 or worse treatment-related adverse events included hypertension (n=12; 23%), diarrhoea (n=5; 10%), fatigue (n=5; 10%), and increased alanine aminotransferase concentration (n=4; 8%; table 2). No treatment-related deaths occurred. 28 (54%) patients had serious adverse events (appendix p 4). The most common serious adverse events included diarrhoea (n=6; 12%), dyspnoea (n=4; 8%), colitis (n=3; 6%), increased alanine aminotransferase concentration (n=2; 4%), fatigue (n=2; 4%), pleural effusion (n=2; 4%), small intestinal obstruction (n=2; 4%), and vomiting (2; 4%; appendix p 4).

The most common possibly immune-related adverse events included diarrhoea (n=15; 29%), increased alanine aminotransferase concentration (n=9; 17%), increased aspartate aminotransferase concentration (n=7; 13%), hypothyroidism (n=7; 13%), and fatigue (n=6; 12%; table 3). Grade 3–4 potentially immune-related adverse events occurred in ten patients (patients could have more than one adverse event): diarrhoea (n=4; 8%), increased alanine aminotransferase concentration (n=2; 4%), increased aspartate aminotransferase concentration (n=2; 4%), fatigue (n=2; 4%), adrenal insufficiency (n=1; 2%), autoimmune colitis (n=1; 2%), colitis (n=1; 2%), diabetes (n=1; 2%), hepatitis (n=1; 2%), lymphocyte count decreased (n=1; 2%), muscular weakness (n=1; 2%), pneumonitis (n=1; 2%), and weight decreased (n=1; 2%; table 3).

Notable alterations in haematological parameters based on laboratory reports during the entire study period included development of lymphopenia (a shift from grade 0 to grade 3 [n=3, 6%], and from grade 1 to grade 3 [n=1; 2%]), and in absolute neutrophil count (a shift from grade 0 to grade 3 [n=2; 4%]). Grade 3 laboratory parameters based on laboratory reports during the entire study period included alanine aminotransferase elevation (n=2; 4%), hypercalcaemia (n=1; 2%),

	Grade 1–2	Grade 3*
Any adverse event	23 (44%)	10 (19%)
Diarrhoea	11 (21%)	4 (8%)
Increased alanine aminotransferase concentration	7 (13%)	2 (4%)
Increased aspartate aminotransferase concentration	5 (10%)	2 (4%)
Hypothyroidism	7 (13%)	0
Fatigue	4 (8%)	2 (4%)
Decreased appetite	5 (10%)	0
Hyperthyroidism	5 (10%)	0
Pruritus	5 (10%)	0
Rash	5 (10%)	0
Weight decreased	4 (8%)	1 (2%)
Arthralgia	4 (8%)	0
Colitis	2 (4%)	1 (2%)
Dyspnoea	3 (6%)	0
Nausea	3 (6%)	0
Anaemia	2 (4%)	0
Blood creatinine concentration increased	2 (4%)	0
Chills	2 (4%)	0
Cough	2 (4%)	0
Headache	2 (4%)	0
Hypoalbuminaemia	2 (4%)	0
Lymphocyte count decreased	2 (4%)	1 (2%)
Neutrophil count decreased	2 (4%)	0
Paraesthesia	2 (4%)	0
Pyrexia	2 (4%)	0
Vomiting	2 (4%)	0
White blood cell count decreased	2 (4%)	0

Data are n (%) of all 52 participants. The table lists maximum grade adverse events reported at grades 1–2 in at least two patients and grade 3 events. One (2%) patient had a grade 4 hyperuricaemia event. No grade 5 immune-related adverse events were reported. *One patient could have had one or more adverse events. Six patients received steroids for presumed immune-related adverse events.

Table 3: **Potentially immune-related adverse events related to pembrolizumab in all patients (n=52)**

	All patients (n=52)
Patients with baseline assessment	52 (100%)
Patients with measurable disease at baseline	52 (100%)
Best overall response	
Complete response	4 (8%)
Partial response	34 (65%)
Stable disease	8 (15%)
Progressive disease	3 (6%)
Indeterminate*	3 (6%)
Objective responses†	38 (73%; 59·0–84·4)

Data are n (%) or n (%; 95% CI). *Stable disease or partial response not confirmed, or no follow-up scans available. †Objective response was defined as the proportion of patients with a confirmed complete response or confirmed partial response according to Response Evaluation Criteria in Solid Tumors (version 1.1) definitions, relative to the response-evaluable population. Confirmed responses were those responses that persisted on repeat tumour assessments for at least 4 weeks after initial documentation or response. Otherwise, the patient was counted as a non-responder in the assessment of objective response.

Table 4: **Best overall response**

hyperglycaemia (n=5; 10%) hyperkalaemia (n=1; 2%), hypermagnesaemia (n=1; 2%), hypokalaemia (n=3; 6%), hyponatraemia (n=4; 8%), and hypophosphataemia (n=7; 13%). Urinalysis abnormalities (tests were semiquantitative so grades were quantified only if needed) reported during the entire study period included abnormalities in urine blood or haemoglobin (n=11; 21%), urine glucose (n=9; 17%), and urine protein (n=25; 48%).

At a median follow-up of 20·4 months (IQR 19·1–21·7), 38 (73%; 95% CI 59·0–84·4) patients had an objective response to treatment: four (8%) had a complete response (table 4, figure 2A, appendix p 5) and 34 (65%) had a partial response (table 4, figure 2A); eight (15%) patients had stable disease (table 4, figure 2A). As shown in figure 2A, more than 90% of patients (48 [94%] of the 51 patients represented on the figure) experienced some degree of tumour shrinkage. Responses were observed in 18 (75%) of 24 patients with favourable-risk disease, and 18 (69%) of 26 patients with intermediate-risk or poor-risk disease. Except in one case, continued treatment beyond disease progression was characterised by stabilisation or slow continued progression of disease rather than regression (figure 2B). Among responders (n=38), median time to response was 2·8 months (IQR 2·7–3·9), and median duration of tumour response was 18·6 (95% CI 15·1–not reached) months.

In the 52 patients treated, 20 progression-free survival events (objective tumour progression or on-study death due to any cause) were reported (figure 3). Median progression-free survival was 20·9 months (95% CI 15·4–not evaluable; figure 3). Ten patients who discontinued treatment because of toxicity were censored even though their disease had not progressed (five were still responding to treatment and five were not) and were only followed up for overall survival analysis. Median overall survival was not reached at the median follow-up period of 20·4 months (IQR 19·1–21·7); with deaths reported in six patients (four [8%] due to the disease under study and two [4%] for unknown reasons; figure 4). The probability of being alive at 18 months was 93·9% (95% CI 82·3–98·0; figure 4).

In our analysis of biomarkers in tumour biospecimens, nine (21%) of 43 evaluable tumour biospecimens were positive for PD-L1 and 34 (79%) were negative for PD-L1. An additional five collected tumour biospecimens had insufficient material for the analysis (four tumour samples were either not submitted or did not contain tumour cells). Of the nine patients who were positive for PD-L1, eight (89%) had a partial response and one (11%) had an

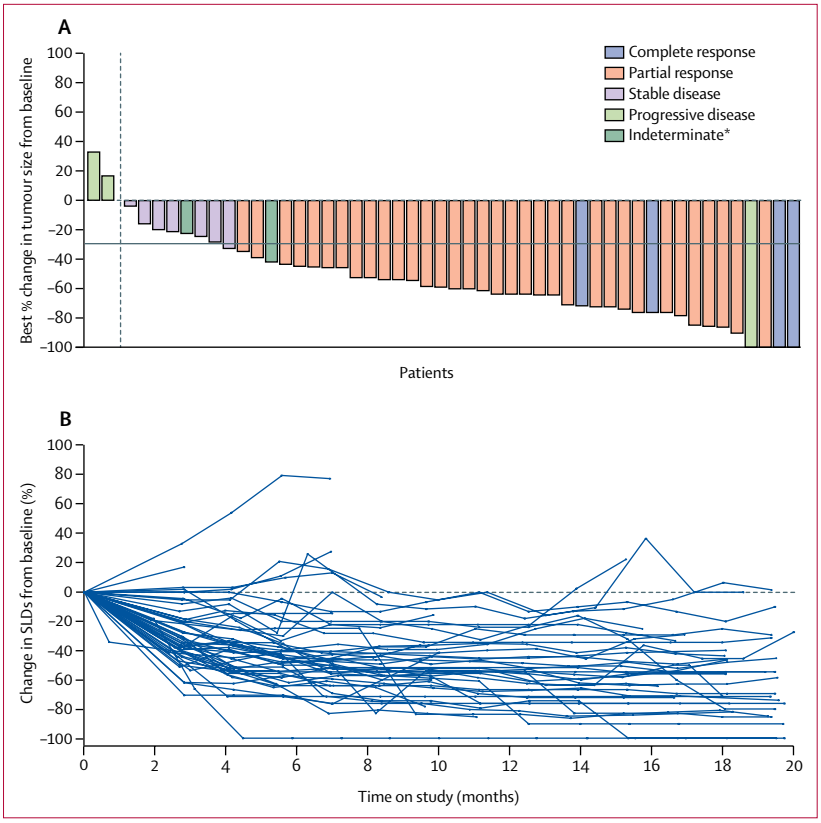

Figure 2: **Percentage change in (A) tumour burden by best response and (B) lesion diameters over time**
(A) Percentage change in tumour burden by best response. The horizontal line at –30% change in tumour size from baseline represents the RECIST version 1.1 cutoff to define partial response or complete response. One patient with stable disease had no change and so was not visible. Another patient, labelled indeterminate, had no follow-up and was excluded from the plot. The patient with progressive disease as best response and 100% tumour shrinkage had an increased size of one lesion that indicated progressive disease on his second scan. This patient remained on treatment and on day 417 met partial response criteria; on day 669 the patient had 100% tumour shrinkage and a complete response. (B) Percentage change in lesion diameters over time. Two patients who had a complete response but do not appear on the chart achieved complete response after months 21 and 22. SLD of all target lesions was used for tumour size calculation at baseline and at all visits. Maximal change in lesion diameters as percentage change was plotted for each patient. SLD=sum of the lesion diameter. *Stable disease or partial response not confirmed, or no follow-up scans available.

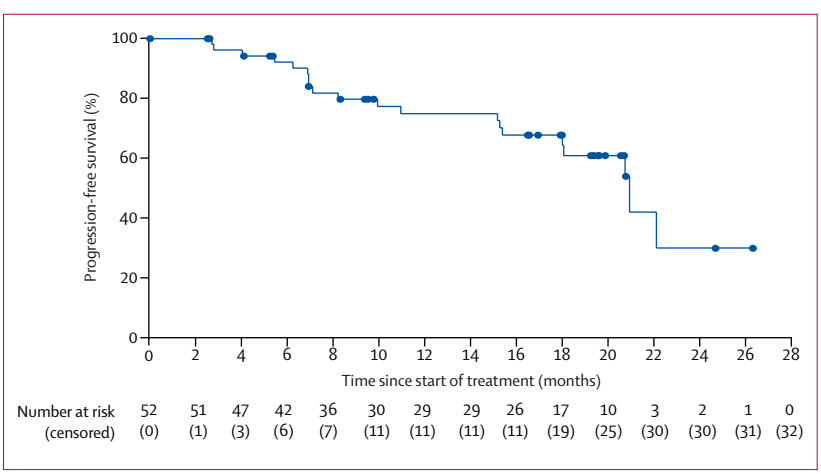

Figure 3: **Progression-free survival**
Points on the curve represent censored patients.

indeterminate response. Of the 34 patients who were negative for PD-L1, four (12%) had a complete response, 20 (59%) had a partial response, six (18%) had stable disease, two (6%) had progressive disease, and two (6%) had an indeterminate response. Median progression-free survival was 22·1 months (95% CI 15·2–not evaluable) for patients with PD-L1-negative tumours and 20·7 months (8·2–not evaluable) for patients with PD-L1-positive tumours. The results from pharmacokinetics, immunogenicity (anti-drug antibodies), pre-dose and post-dose serum biomarkers, and whole blood biomarkers, (all secondary endpoints) will be reported separately.

Discussion

This phase 1b study showed that the combination of axitinib and pembrolizumab at nearly the full planned doses of each drug is tolerable in patients with treatment-naive advanced renal cell carcinoma. This outcome contrasts with the toxicities reported in other clinical studies combining pembrolizumab with pazopanib or nivolumab with sunitinib or pazopanib.[12,13] In particular, fewer liver function test abnormalities or incidences of fatigue were reported in this study than in the previous studies. For example, grade 3–4 elevated alanine aminotransferase was reported in 8% of patients in our study compared with 18% of patients treated with nivolumab plus sunitinib, 20% of patients treated with nivoumab plus pazopanib, and 60–70% of patients treated with pembrolizumab plus pazopanib.[12,13] Of note, axitinib is a more selective inhibitor of VEGFR than sunitinib and pazopanib, which are multitargeted TKIs. The safety profile with axitinib and pembrolizumab is more similar to that seen with the combination of atezolizumab (an anti-PD-L1 drug) plus bevacizumab, another selective inhibitor of the VEGF pathway.[8] PD-1 pathway inhibitors could possibly enhance the off-target effects of the other TKIs, suggesting that more selective combination partners would be preferable to multitargeted TKIs.

The adverse events reported in this study seem to be largely related to axitinib,[23] although some potentially true immune-related adverse events were reported, including colitis and thyroiditis related to pembrolizumab. Because of overlapping toxicities, management of the diarrhoea or liver function test abnormalities might be challenging because these adverse events could result from either axitinib or pembrolizumab treatment. The fact that diarrhoea was improved in many patients with anti-diarrhoeal medications or holding or reducing the axitinib dose (data not shown), and that transaminitis improved with holding and reducing axitinib (data not shown), suggests that these adverse events were a result of an enhanced toxicity of axitinib rather than a true immune-related adverse event predominantly due to pembrolizumab. Typically, immune-related adverse events do not resolve quickly in the absence of immunosuppressive drugs, further supporting the contention that most of the observed toxicity was related to enhanced

 Published online February 10, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30081-0

axitinib toxicity, but not to the degree seen with the less selective VEGFR pathway blockers.

The antitumour activity of the combination treatment is unprecedented and superior to that expected from axitinib or PD-1 pathway inhibitor monotherapy. The proportion of patients who achieved an objective response was 73%, with complete responses in 8% of patients, tumour shrinkage in more than 90% of patients, and only two patients without tumour shrinkage or stable disease, as well as a median progression-free survival exceeding 20 months, which was longer than the median progression-free survival of 10–15 months reported with axitinib monotherapy in two first-line trials[15,16] in patients with renal cell carcinoma. Although no data are available for pembrolizumab monotherapy in patients with renal cell carcinoma, nivolumab monotherapy produced an objective response of 13% in a small subset of patients with previously untreated renal call carcinoma, and in 20–30% patients with VEGF pathway blockade-refractory disease.[6,7,9,24] Furthermore, atezolizumab monotherapy led to objective responses in 25% of patients and median progression-free survival of 6 months (95% CI 5·4–13·6) in patients who were treatment-naive, and objective responses in 15% of patients and median progression-free survival of 6 months (3·9–8·2) in patients who had been previously treated.[8,25] Together, these results suggest the antitumour efficacy with axitinib and pembrolizumab is at least additive and possibly synergistic.

Although the objective response results and median progression-free survival with axitinib and pembrolizumab are encouraging, it should be noted that these outcomes could have been even better if the protocol had not dictated censoring of patients who discontinued treatment because of toxicity at the time of treatment discontinuation, even if these patients had tumour shrinkage. Conversely, the patient population in this study might differ from the renal cell carcinoma population generally included in renal cell carcinoma clinical trials because all patients had previous nephrectomy (at a median of 2 years before enrolment), 75% had ECOG performance status 0, and very few patients had poor-risk disease as according to the international Metastatic Database Consortium criteria (46% of patients had favourable-risk disease and 44% had intermediate-risk disease).[26]

Although half of the patients in our study had intermediate or poor risk features, our trial population was a more favourable prognostic population than typically included in front-line renal cell carcinoma trials and therefore cross-trial comparisons should be interpreted with caution. However, the activity in terms of objective responses achieved with axitinib and pembrolizumab is higher than that reported for other combinations of VEGF pathway inhibitors plus checkpoint inhibitors (ie, nivolumab–sunitinib or nivolumab–pazopanib, pembrolizumab–pazopanib, atezolizumab–bevacizumab, and axitinib–avelumab).[8,12–14] Whether the efficacy is due to the differences in the checkpoint inhibitor, the VEGF pathway inhibitor, the ability to keep patients on treatment due to lower toxicity, patient selection, or just small numbers of patients in these studies remains to be determined. Notably, based on the results of this phase 1b trial, the US FDA granted the combination of axitinib–pembrolizumab a break-through status.[27]

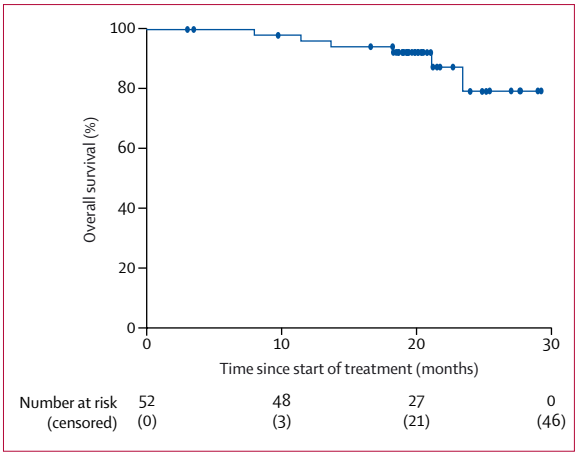

Figure 4: **Overall survival**
Points on the curve represent censored patients.

Although this treatment regimen does seem to exhibit high antitumour activity, it does involve the administration of first-line and second-line treatment approaches together for a potentially longer period of time than would be typical if these drugs were used in a sequence. This increase in treatment time might have cost implications for the therapy, since both drugs are given for longer dosing periods when in combination than they would if given as monotherapies. Whether the combination works better than a sequence of VEGF pathway inhibitor followed by an anti-PD-1 therapy and in a less heavily selected patient population awaits the completion of phase 3 trials, such as the ongoing KEYNOTE-426 phase 3, randomised, open-label trial of axitinib plus pembrolizumab versus sunitinib mono-therapy in previously untreated patients with advanced or metastatic renal cell carcinoma (NCT02853331). Notably, the Checkmate 209-214 trial reported that the combination of nivolumab and ipilimumab (an anti-CTLA4 antibody) produced more responses, longer response durations, and superior overall survival than sunitinib monotherapy in patients with intermediate-risk and poor-risk renal cell carcinoma,[28] suggesting that the axitinib plus pembrolizumab combination might also need to be compared with the sequence of the nivolumab plus ipilimumab combination followed by a VEGF pathway inhibitor at time of disease progression.

Antiangiogenic therapies (sunitinib or bevacizumab) have the ability to not only inhibit angiogenesis but also block the accumulation of immunosuppressive cells and promote influx of effector T cells into tumours.[29–31]

Although no specific data exist for the ability of axitinib to modify the tumour microenvironment in renal cell carcinoma, its ability to inhibit myeloid-derived suppressor cells in melanoma[32] suggests that it is likely to work in a similar way to other VEGF inhibitors. This biology suggests that anti-VEGF treatment might enhance the immune effects of checkpoint inhibitors. To what extent such an immune effect is responsible for the apparent synergistic antitumour outcomes seen with axitinib and pembrolizumab is difficult to discern. Although responses were remarkably durable in patients treated with this combination, the study did not allow discontinuation of axitinib in responding patients and, therefore, it was impossible to determine to what extent these responses would be maintained off-treatment—a hallmark of an activated antitumour immune response. Although PD-L1 expression (either by the tumour or tumour-associated immune cells) was associated with improved efficacy for the combinations of nivolumab–ipilimumab and bevacizumab–atezolizumab, another sign of a possible immune mechanism, the high degree of antitumour activity with our regimen coupled with the low frequency of PD-L1 expression (19%) prohibited any clinically meaningful assessments of response by PD-1 expression level in our study. Similarly, the efficacy of VEGF inhibitor therapy, including axitinib, has been linked to development of hypertension;[33] however, the high degree of antitumour activity, low frequency of grade 3 hypertension, and small study size precluded a correlation of either tumour response or progression-free survival with this potential predictor of anti-VEGF therapy benefit. Future research should unravel the biology of VEGF inhibitor and checkpoint inhibitor combinations in renal cell carcinoma to optimise treatment schedules and determine how long each treatment approach should be given to particular groups of patients.

In conclusion, this trial shows that the combination of axitinib and pembrolizumab is safe and tolerable in patients with treatment-naive advanced renal cell carcinoma, and also exhibits unprecented antitumour activity. Future research should focus on investigating the mechanism of the potential synergistic effects of axitinib and pembrolizumab, and whether an immunotherapy-only approach (including combinations) enriched by the appropriate biomarkers, followed by VEGFR TKI salvage, might produce more durable off-treatment responses or whether administering VEGFR TKI monotherapy followed by PD-1 and PD-L1 pathway blockade might produce superior or equivalent results.

Contributors

MBA, TKC, JCT, BR, KCF, ML, and IP conceived and designed the study. MBA, ERP, IP, MNF, DFM, DCC, UV, SG, TEO, JCT, KCF, ML, and TKC collected and assembled the data. MBA, TKC, JCT, BR, KCF, and ML analysed and interpreted the data. All authors participated in writing the paper and approved the final version of the paper.

Declaration of interests

JCT, BR, ML, and KCF are employees of and own stock in Pfizer. MBA declares receiving fees for consulting from Bristol-Myers Squibb (BMS), Pfizer, Novartis, Genentech-Roche, Merck, and Eisai. ERP declares receiving fees for consulting from AstraZeneca, BMS, Clovis, Eli Lilly and Company, Exelexis, Genentech, Horizon Pharma, Inovio, Novartis, Pfizer, and Roche, and grant support to her institution has been received from AstraZeneca, BMS, Merck, Peloton, Pfizer, GlaxoSmithKline (GSK), Dendreon, Aveo, Acceleron, and Eli Lilly Inc. MNF has received research funding from BMS, Exelixis, Eisai, Genentech, Acceleron, Merck, Prometheus, Nektar, Alkermes, and Pfizer, and has served on speakers bureaus for Exelixis. DFM declares receiving fees for consulting from BMS, Pfizer, Novartis, Genentech-Roche, Merck, Eisai, Array BioPharm, Prometheus, and Exelixis. SG declares receiving fees for consulting and serving on advisory boards from Pfizer, Exelixis, BMS, Novartis, Bayer, Janssen, Corvus, and AstraZeneca, and institutional grant support from BMS, Novartis, Bayer, Pfizer, Merck, and Agensys. TKC declares receiving fees for consulting and for serving on advisory boards from GSK, Novartis, Pfizer, Merck, AstraZeneca, Bayer, Genentech, Exelixis, Eisai, Cerulean, Foundation Medicine Inc, Corvus, and Prometheus, and grant support through his institution from BMS, GSK, Novartis, Exelixis, Pfizer, Merck, Roche, AstraZeneca, TRACON Pharmaceuticals, and Peloton. DCC declares receiving fees for consulting from Pfizer, Genentech, Prometheus, BMS, and Exelixis. UV declares research support from Astellas, Novartis, and Exelixis and consulting fees from Pfizer, Bayer, and BMS. All other authors declare no competing interests.

Acknowledgments

This study is sponsored by Pfizer Inc in collaboration with Merck & Co, Inc, Kenilworth, NJ, USA. Medical writing support was provided by Vardit Dror of Engage Scientific Solutions, and was funded by Pfizer.

References

1 Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer* 2008; **8:** 592–603.
2 Grepin R, Pages G. Molecular mechanisms of resistance to tumour anti-angiogenic strategies. *J Oncol* 2010; **2010:** 835680.
3 Ahmadzadeh M, Johnson LA, Heemskerk B, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood* 2009; **114:** 1537–44.
4 Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol* 2008; **8:** 467–77.
5 Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res* 2006; **66:** 3381–85.
6 McDermott DF, Drake CG, Sznol M, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *J Clin Oncol* 2015; **33:** 2013–20.
7 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366:** 2443–54.
8 Atkins MB, McDermott DF, Powles T, et al. IMmotion150: a phase II trial in untreated metastatic renal cell carcinoma (mRCC) patients (pts) of atezolizumab (atezo) and bevacizumab (bev) vs and following atezo or sunitinib (sun). *Proc Am Soc Clin Oncol* 2017; **35** (15 suppl): 4505 (abstr).
9 Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; **373:** 1803–13.
10 Dirkx AE, oude Egbrink MG, Castermans K, et al. Anti-angiogenesis therapy can overcome endothelial cell anergy and promote leukocyte-endothelium interactions and infiltration in tumors. *FASEB J* 2006; **20:** 621–30.
11 Yasuda S, Sho M, Yamato I, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. *Clin Exp Immunol* 2013; **172:** 500–06.
12 Amin A, Plimack ER, Infante JR, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC). *Proc Am Soc Clin Oncol* 2014; **32** (suppl 15)**:** 5010 (abstr).
13 Chowdhury S, McDermott DF, Henner Voss M, et al. A phase I/II study to assess the safety and efficacy of pazopanib (PAZ) and pembrolizumab (PEM) in patients (pts) with advanced renal cell carcinoma (aRCC). *Proc Am Soc Clin Oncol* 2017; **35** (15 suppl): 4506 (abstr).

14 Choueiri TK, Larkin JMG, Oya MF, et al. First-line avelumab + axitinib therapy in patients (pts) with advanced renal cell carcinoma (aRCC): results from a phase Ib trial. *Proc Am Soc Clin Oncol* 2017; **35** (15 suppl): 4504 (abstr).

15 Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol* 2013; **14:** 1233–42.

16 Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol* 2013; **14:** 1287–94.

17 Atkins MB, Choueiri TK, Hodi FS, et al. Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): data from the KEYNOTE-029 phase 1 study. *Proc Am Soc Clin Oncol* 2015; **33** (15 suppl): 3009 (abstr).

18 Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015; **372:** 2018–28.

19 Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013; **369:** 134–44.

20 Pfizer. Inlyta (axitinib) prescribing information. New York, NY: Pfizer Inc, 2012.

21 Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387:** 1540–50.

22 Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clin Trials* 2010; **7:** 653–63.

23 Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011; **378:** 1931–39.

24 Choueiri TK, Fishman MN, Escudier B, et al. Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma. *Clin Cancer Res* 2016; **22:** 5461–71.

25 McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: long-term safety, clinical activity, and immune correlates from a phase Ia study. *J Clin Oncol* 2016; **34:** 833–42.

26 Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; **27:** 5794–99.

27 Merck Sharp & Dohme Corp. http://www.mrknewsroom.com/news-release/corporate-news/merck-announces-second-quarter-2017-financial-results (accessed Feb 2, 2018).

28 Escudier B, Tannir NM, McDermott DF, et al. CheckMate 214: efficacy and safety of nivolumab plus ipilimumab vs sunitinib for treatment-naive advance or metastatic renal cell carcinoma, including IMDC risk and PD-L1 expression subgroups. *Ann Oncol* 2017; **28:** LBA5 (abstr).

29 Katoh H, Watanabe M. Myeloid-derived suppressor cells and therapeutic strategies in cancer. *Mediators Inflamm* 2015; **2015:** 159269.

30 Lanitis E, Irving M, Coukos G. Targeting the tumor vasculature to enhance T cell activity. *Curr Opin Immunol* 2015; **33:** 55–63.

31 Voron T, Marcheteau E, Pernot S, et al. Control of the immune response by pro-angiogenic factors. *Front Oncol* 2014; **4:** 70.

32 Zhang X, Fang X, Gao Z, et al. Axitinib, a selective inhibitor of vascular endothelial growth factor receptor, exerts an anticancer effect in melanoma through promoting antitumor immunity. *Anticancer Drugs* 2014; **25:** 204–11.

33 Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. *Clin Cancer Res* 2011; **17:** 3841–49.