Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial

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Summary

Background The combination of an immune checkpoint inhibitor and a VEGF pathway inhibitor to treat patients with advanced renal-cell carcinoma might increase the clinical benefit of these drugs compared with their use alone. Here, we report preliminary results for the combination of avelumab, an IgG1 monoclonal antibody against the programmed cell death protein ligand PD-L1, and axitinib, a VEGF receptor inhibitor approved for second-line treatment of advanced renal-cell carcinoma, in treatment-naive patients with advanced renal-cell carcinoma.

Methods The JAVELIN Renal 100 study is an ongoing open-label, multicentre, dose-finding, and dose-expansion, phase 1b study, done in 14 centres in the USA, UK, and Japan. Eligible patients were aged 18 years or older (≥20 years in Japan) and had histologically or cytologically confirmed advanced renal-cell carcinoma with clear-cell component, life expectancy of at least 3 months, an Eastern Cooperative Oncology Group performance status of 1 or less, received no previous systemic treatment for advanced renal cell carcinoma, and had a resected primary tumour. Patients enrolled into the dose-finding phase received 5 mg axitinib orally twice daily for 7 days, followed by combination therapy with 10 mg/kg avelumab intravenously every 2 weeks and 5 mg axitinib orally twice daily. Based on the pharmacokinetic data from the dose-finding phase, ten additional patients were enrolled into the dose-expansion phase and assigned to this regimen. The other patients in the dose-expansion phase started taking combination therapy directly. The primary endpoint was dose-limiting toxicities in the first 4 weeks (two cycles) of treatment with avelumab plus axitinib. Safety and antitumour activity analyses were done in all patients who received at least one dose of avelumab or axitinib. This trial is registered with ClinicalTrials.gov, number NCT02493751.

Findings Between Oct 30, 2015, and Sept 30, 2016, we enrolled six patients into the dose-finding phase and 49 into the dose-expansion phase of the study. One dose-limiting toxicity of grade 3 proteinuria due to axitinib was reported among the six patients treated during the dose-finding phase. At the cutoff date (April 13, 2017), six (100%, 95% CI 54–100) of six patients in the dose-finding phase and 26 (53%, 38–68) of 49 patients in the dose-expansion phase had confirmed objective responses (32 [58%, 44–71] of all 55 patients). 32 (58%) of 55 patients had grade 3 or worse treatment-related adverse events, the most frequent being hypertension in 16 (29%) patients and increased concentrations of alanine aminotransferase, amylase, and lipase, and palmar-plantar erythrodysaesthesia syndrome in four (7%) patients each. Six (11%) of 55 patients died before data cutoff, five (9%) due to disease progression and one (2%) due to treatment-related autoimmune myocarditis. At the end of the dose-finding phase, the maximum tolerated dose established for the combination was avelumab 10 mg/kg every 2 weeks and axitinib 5 mg twice daily.

Interpretation The safety profile of the combination avelumab plus axitinib in treatment-naive patients with advanced renal-cell carcinoma seemed to be manageable and consistent with that of each drug alone, and the preliminary data on antitumour activity are encouraging. A phase 3 trial is assessing avelumab and axitinib compared with sunitinib monotherapy.

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Introduction

Around 338 000 cases of renal-cell carcinoma are diagnosed worldwide every year,[1] and approximately 30% of patients have advanced-stage or metastatic disease at the time of diagnosis.[2] Approved first-line therapies for patients with surgically unresectable, relapsed, or metastatic renal-cell carcinoma with predominantly clear cell histology include the antiangiogenic VEGF-receptor (VEGFR) tyrosine-kinase inhibitors (TKIs) pazopanib and sunitinib and the VEGFR-ligand monoclonal antibody bevacizumab in combination with interferon alfa.[3] For patients with poor prognosis, including those with unresectable, relapsed, or metastatic disease less than 1 year from diagnosis, poor performance status scores,

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Research in context

Evidence before this study

Before 2005, the standard-of-care treatment options for patients with advanced renal-cell carcinoma were interferon alfa and high-dose interleukin 2 and achieved little clinical benefit with notable toxicity. Outcomes have since been improved substantially due to the development and approval of multiple targeted therapies. Nevertheless, durable and complete responses are not common, and most patients eventually develop resistance to targeted therapies and have disease progression or metastatic disease. Single-agent treatments with monoclonal antibodies that block the interaction between the programmed cell death protein PD-1 and its ligand PD-L1 have shown activity in heavily pretreated patients with advanced renal-cell carcinoma, including those with disease that progressed after receiving angiogenesis inhibitors. Clinical trials investigating combinations of antibodies against PD-L1 or PD-1 and VEGFR tyrosine-kinase inhibitors have shown improved antitumour activity over single-agent therapy, probably because of each drug's distinct but complementary mechanistic effects, with safety profiles similar to those of the respective monotherapies.

Added value of this study

To the best of our knowledge, the JAVELIN Renal 100 trial is the first to investigate the safety and antitumour activity of first-line avelumab, a human IgG1 monoclonal antibody against PD-L1 that inhibits interactions with PD-1, in combination with axitinib, a VEGFR TKI approved for second-line or later treatment of advanced renal-cell carcinoma. The overall response and durability of responses in our study are encouraging and warrant further study of this drug combination.

Implications of all the available evidence

First-line combination treatment with avelumab and axitinib for advanced renal-cell carcinoma showed encouraging antitumour activity with a manageable adverse event profile. These findings support the pivotal, randomised, phase 3 JAVELIN Renal 101 trial (NCT02684006), which is comparing combined avelumab and axitinib with sunitinib monotherapy as first-line treatment for advanced renal-cell carcinoma.

low haemoglobin concentrations, high calcium or lactate dehydrogenase concentrations in serum, and more than one metastatic organ site, the mTOR pathway inhibitor temsirolimus is an option.[3] Approved second-line or later targeted therapies for patients with advanced disease include monotherapy with the VEGF pathway inhibitors axitinib or cabozantinib, and the combination of the mTOR inhibitor everolimus with the VEGFR TKI lenvatinib.[3] Although many patients with advanced renal-cell carcinoma who receive these approved therapies show clinical benefit, the regimens are associated with severe adverse events, and in most patients disease will eventually progress.[4,5] Therefore, novel therapies and regimens that can achieve clinical activity and survival improvements with manageable toxicity profiles are needed.

Antibodies that target the interaction between the programmed cell death protein (PD-1) on T cells and its ligand (PD-L1) expressed on tumour cells prevent downregulation of cellular immune responses in the tumour microenvironment.[6] Studies of the monoclonal antibody against PD-1, nivolumab, used alone or in combination,[7–10] and of atezolizumab, a monoclonal antibody against PD-L1,[11] have shown clinical activity and acceptable tolerability in patients with advanced renal-cell carcinoma. Nivolumab is approved as second-line monotherapy after antiangiogenic therapy for these patients.[12]

See Online for appendix

Avelumab, a human IgG1 monoclonal antibody against PD-L1, inhibits interactions between PD-L1 and PD-1.[13] Unlike other PD-L1-targeted antibodies assessed in clinical trials so far, avelumab is unmodified, meaning that it retains the potential to elicit effector-cell functions and might induce antibody-dependent cell-mediated cytotoxicity of tumour cells.[14,15] Avelumab is approved in the USA and the European Union for the treatment of metastatic Merkel-cell carcinoma,[16,17] in Japan for curatively unresectable Merkel-cell carcinoma, and in the USA for advanced urothelial carcinoma in patients whose disease progressed while receiving platinum-containing chemotherapy.[16] The combination of an antibody that inhibits PD-L1 and PD-1 interactions with a targeted antiangiogenic agent might take advantage of complementary mechanisms of action to provide clinical benefit in patients with advanced renal-cell carcinoma that exceeds the effects of the respective drugs alone without increasing associated toxicity. Combinations explored previously in patients with advanced renal-cell carcinoma have involved pembrolizumab (antibody against PD-1) with axitinib,[18] pazopanib,[19] or lenvatinib,[20] and atezolizumab with bevacizumab.[21] In the JAVELIN Renal 100 trial, we are exploring the safety and antitumour activity of avelumab in combination with axitinib in previously untreated patients with advanced renal-cell carcinoma.

Methods

Study design and participants

This open-label, multicentre, dose-finding and dose-expansion, phase 1b trial is being done in 14 centres in the USA, UK, and Japan (appendix p 4). It included a dose-finding phase designed to estimate the maximum tolerated dose (highest tested avelumab and axitinib dose associated with the occurrence of dose-limiting toxic effects in <33% of assessable patients within the first two cycles of treatment) and confirm the recommended phase 2 dose for the combination of avelumab and

axitinib in treatment-naive patients with advanced renal-cell carcinoma through the modified toxicity probability interval method. If the initial dose level had exceeded the maximum tolerated dose, we had prespecified two lower doses to which patients would be randomised for concurrent assessment, but this hypothetical scenario did not occur (appendix p 22).

Eligible patients were aged 18 years or older (≥20 years in Japan), had a life expectancy of at least 3 months, and met the following key inclusion criteria: histologically or cytologically confirmed advanced renal-cell carcinoma with clear-cell component; resected primary tumour; at least one measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1; an available fresh or archival primary tumour specimen; an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 or lower; no previous systemic therapy for advanced renal-cell carcinoma; and adequate haematological, hepatic, and renal functions (see definitions on appendix p 2). Patients were excluded if they had CNS metastases requiring systemic corticosteroid treatment or active autoimmune disease, were pregnant or lactating, or had received systemic corticosteroids at a higher dose than the physiological concentrations within 7 days of enrolment. Patients were not selected based on PD-L1 status.

The trial was done in accordance with the ethics principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent. Three protocol amendments (made on April 22 and Aug 27, 2015, and June 8, 2016) and informed consent forms were approved by an institutional review board or independent ethics committee at each study site (the full list of study sites is shown in the appendix p 4).

Procedures

Patients enrolled into the dose-finding phase received 5 mg axitinib twice daily for 7 days (lead-in period) to allow assessment of any effects of avelumab on axitinib pharmacokinetics, followed by combination therapy with 10 mg/kg avelumab every 2 weeks and 5 mg axitinib twice daily (appendix p 22). Avelumab was administered as 1 h intravenous infusions, and each 5 mg dose of axitinib was provided as an oral tablet to be taken with or without food. Patients enrolled into the dose-expansion phase of the study either started with combination therapy or received the lead-in of axitinib alone followed by combination treatment. All patients continued treatment until confirmed disease progression, unacceptable toxicity, refusal to participate further, or loss to follow-up. Patients with evidence of disease progression who were still experiencing clinical benefit could be considered for continuation of treatment as per the investigator's clinical judgment and after discussion between the investigator and sponsor. Dose reductions for axitinib were allowed within a cycle or in a subsequent cycle in the event of toxicity, based on the treating investigators' judgment, and in line with the prescribing information in the

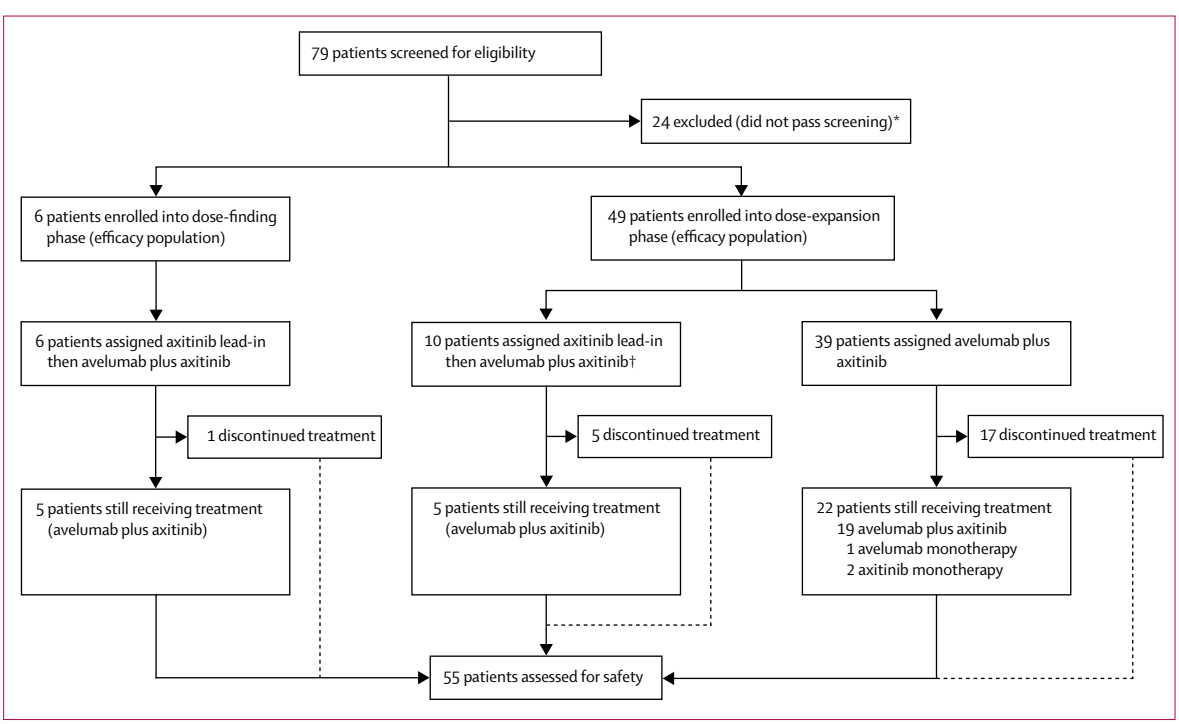

Figure 1: **Trial profile**

*One patient was not included in data outputs because the site reported the wrong date of screening failure. †One patient received only axitinib due to an unrelated adverse event experienced before avelumab administration.

package insert.[22] Dose modifications were not permitted for avelumab, but dose interruptions (omission of the next infusion) were possible if toxicity persisted. The prespecified intrapatient dose omissions for avelumab and dose reductions for axitinib are detailed in the appendix (pp 5–6). If patients developed unacceptable toxicity attributed to one of the study treatments leading to discontinuation, they could continue receiving the other study treatment. Premedication with an antihistamine and paracetamol before each dose of avelumab was mandatory and could be modified at each site as per local treatment guidelines.

Safety was assessed weekly in the first cycle for patients who were started on avelumab plus axitinib and in the first and second cycles for those who received lead-in axitinib followed by avelumab plus axitinib. Thereafter, safety was monitored every 2 weeks in all patients. Safety assessments included monitoring for adverse events and performance status, clinical laboratory tests, and physical examinations. Adverse events were classified and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

	Dose-finding cohort (n=6)	Dose-expansion cohort (n=49)	All patients (n=55)
Age (years)			
Mean (SD)	59·2 (10·6)	60·5 (8·6)	60·3 (8·7)
Median (IQR)	59·5 (50·0–68·0)	60·0 (55·0–68·0)	60·0 (55·0–68·0)
<65	4 (67%)	34 (69%)	38 (69%)
≥65	2 (33%)	15 (31%)	17 (31%)
Sex			
Male	4 (67%)	38 (78%)	42 (76%)
Female	2 (33%)	11 (22%)	13 (24%)
Ethnicity			
White	6 (100%)	38 (78%)	44 (80%)
Asian	0	6 (12%)	6 (11%)
Black or African American	0	3 (6%)	3 (6%)
Other	0	1 (2%)	1 (2%)
Unknown	0	1 (2%)	1 (2%)
ECOG performance status score			
0	5 (83%)	31 (63%)	36 (66%)
1	1 (17%)	18 (37%)	19 (35%)
MSKCC risk category			
Favourable	1 (17%)	27 (55%)	28 (51%)
Intermediate	4 (67%)	21 (43%)	25 (46%)
Poor	0	1 (2%)	1 (2%)
Missing	1 (17%)	0	1 (2%)
Number of target tumour sites			
1	3 (50%)	22 (45%)	25 (46%)
2	3 (50%)	20 (41%)	23 (42%)
3	0	7 (14%)	7 (13%)

Data are number (%) unless stated otherwise. Total percentage values might sum to >100% because of rounding. All patients had stage IV renal-cell carcinoma at the time of study entry. ECOG=Eastern Cooperative Oncology Group. MSKCC=Memorial Sloan Kettering Cancer Center.

Table 1: **Baseline characteristics**

Tumour assessments by CT or MRI were done in all known or suspected disease sites (eg, chest, abdomen, and pelvis). Imaging of the brain with CT or MRI was done at baseline or any time during the study when brain metastasis was suspected. Bone scanning or ^{18}F-fluorodeoxyglucose PET was done at baseline and, if bone metastasis was present, every 12 weeks thereafter. Antitumour activity was assessed radiologically at baseline, every 6 weeks up to 1 year after the first dose, and every 12 weeks thereafter, with responses classified per RECIST version 1.1. We assessed antitumour activity in terms of objective responses, tumour shrinkage, disease control, time to tumour response, duration of response, progression-free survival, and overall survival (appendix pp 2–3). PD-L1 expression on immune and tumour cells in tumour samples was characterised with an analytical immunohistochemistry assay (Ventana PD-L1 [SP263] kit, Ventana Medical Systems, Tucson, AZ, USA). Exploratory scoring algorithms allowed for PD-L1 staining of any intensity, and we investigated responses in subsets of patients defined by PD-L1 expression on tumour or immune cells of at least 1%, 5%, 25%, or 50%.

Outcomes

The primary endpoint of this study was dose-limiting toxicity within the first 4 weeks (two cycles) of treatment with avelumab in combination with axitinib. Dose-limiting events were defined as adverse events in the first 4 weeks that were judged to be attributable to one agent or both in combination. Relevant haematological events were grade 4 anaemia, grade 4 neutropenia lasting longer than 7 days, febrile neutropenia (absolute neutrophil count $<1{\cdot}0\times10^9$/L with temperature >38·3°C on one measurement or ≥38·0°C for >1 h), grade 3 or worse neutropenic infection, grade 3 or worse thrombocytopenia with bleeding, or grade 4 thrombocytopenia. Relevant non-haematological events, including those not identified by laboratory tests, were any grade 3 or worse toxicity except transient (≤6 h) grade 3 flu-like symptoms or fever that could be controlled by medical management, transient (≤24 h) grade 3 fatigue, local reaction, or headache that resolved to grade 1 or better, grade 3 or 4 nausea and vomiting controlled by optimum medical therapy within 72 h, grade 3 hypertension controlled by medical therapy, grade 3 diarrhoea or grade 3 skin toxicity that resolved to at least grade 1 within 7 days of starting medical management (eg, immunosuppressants), any grade 3 or worse amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis, and tumour flare phenomenon defined as local pain, irritation, or rash localised at sites of known or suspected tumours; grade 3 or 4 increases in alanine aminotransferase or aspartate aminotransferase concentrations concurrent with grade 2 increase in total bilirubin concentration (liver function); non-haematological grade 3 or worse laboratory abnormality that needed medical intervention or led to admission to hospital

(excluding single laboratory values out of normal range judged unlikely to be related to trial treatment by the investigator, without clinical correlates, and that resolved to grade ≤1 within 7 days with adequate medical management); and any event related to the trial treatment preventing completion of at least 75% of doses of axitinib or two infusions of avelumab during the first two cycles of combined therapy.

Secondary endpoints included adverse events and laboratory abnormalities (graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03); vital signs (measured by blood pressure and pulse); confirmed objective response (complete response, defined as disappearance of all target lesions and reduction in short axis to <10 mm of any pathological lymph nodes, or partial response, defined as ≥30% decrease in the sum of diameters of target lesions compared with baseline) according to RECIST version 1.1 from first dose of study drug to first documentation of progressive disease or death from any cause; disease control (best overall response among complete response, partial response, non-complete response or non-progressive disease, or stable disease per RECIST version 1.1) from first dose of study drug until first documentation of progressive disease or death from any cause; time to tumour response, defined as the time from first dose of study drug to the first documented objective response that was later confirmed; duration of response, defined as the time from the first documented objective response that was later confirmed to the date of disease progression or death from any cause; progression-free survival, defined as the time from first dose of study drug to the date of the first documentation of disease progression or death from any cause, whichever occurred first; overall survival, defined as the time from the first dose of study drug to the date of death from any cause; and tumour PD-L1 expression status. The full list of predefined secondary endpoints for this trial is in the appendix (p 23).

Statistical analysis

The sample size for the dose-finding phase could not be determined in advance of the study because of the unknown safety profile of combined avelumab and axitinib and the dynamic nature of dose allocation. Rather, it arose from logistic feasibility and was not entirely driven by statistical considerations. We estimated that a sample size of 40 patients for the dose-expansion phase would provide at least 90% probability of one or more adverse events occurring if the true incidence of the event in the population was 6% or more. Based on the emerging pharmacokinetic data after the dose-finding phase was complete, we decided to enrol ten additional patients into the dose-expansion group who would receive lead-in therapy with 5 mg axitinib orally twice daily for 7 days to further assess the effect of avelumab on the pharmacokinetic profile of axitinib.

Data from all patients who received at least one dose of avelumab and axitinib and had either dose-limiting toxicity during the first two cycles of combination treatment or completed the primary dose-limiting toxicity period for the first two cycles of treatment (4 weeks), and from all patients in the dose-expansion

	All grades	Grade 3	Grade 4	Grade 5
All events	53 (96%)	26 (47%)	5 (9%)	1 (2%)
Diarrhoea	32 (58%)	2 (4%)	0	0
Dysphonia	26 (47%)	0	0	0
Hypertension	26 (47%)	16 (29%)	0	0
Fatigue	25 (46%)	2 (4%)	0	0
PPE syndrome	17 (31%)	4 (7%)	0	0
ALT increased	16 (29%)	4 (7%)	0	0
Rash	16 (29%)	1 (2%)	0	0
AST increased	14 (26%)	1 (2%)	0	0
Hypothyroidism	14 (26%)	0	0	0
Amylase increased	13 (24%)	3 (6%)	1 (2%)	0
Decreased appetite	13 (24%)	1 (2%)	0	0
Mucosal inflammation	13 (24%)	1 (2%)	0	0
Infusion-related reaction*	11 (20%)	1 (2%)	0	0
Lipase increased	11 (20%)	1 (2%)	3 (6%)	0
Nausea	11 (20%)	1 (2%)	0	0
Arthralgia	9 (16%)	1 (2%)	0	0
Weight decreased	9 (16%)	1 (2%)	0	0
Pruritus	8 (15%)	0	0	0
Dysgeusia	7 (13%)	0	0	0
Stomatitis	7 (13%)	0	0	0
Dyspnoea	6 (11%)	0	0	0
Myalgia	6 (11%)	0	0	0
Proteinuria	6 (11%)	2 (4%)	0	0
Vomiting	6 (11%)	0	0	0
Hypophosphataemia	5 (9%)	2 (4%)	0	0
Blood triglycerides increased	4 (7%)	1 (2%)	0	0
Dehydration	3 (6%)	1 (2%)	0	0
Pain in extremity	3 (6%)	1 (2%)	0	0
Drug eruption	1 (2%)	1 (2%)	0	0
Dyslipidaemia	1 (2%)	1 (2%)	0	0
Haematoma	1 (2%)	0	1 (2%)	0
Myocarditis	1 (2%)	0	0	1 (2%)
Pulmonary embolism	1 (2%)	0	1 (2%)	0
Urticaria	1 (2%)	1 (2%)	0	0
Venous thrombosis	1 (2%)	1 (2%)	0	0

Events occurring in ≥10% of patients for all grades, and all grade 3, 4, and 5 events are shown, classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Participants who had more than one event within a category are counted only once in that category. All events refers to the number of patients with any treatment-related adverse events. PPE=palmar-plantar erythrodysaesthesia. ALT=alanine aminotransferase concentration. AST=aspartate aminotransferase concentration. *Refers to the Medical Dictionary for Regulatory Activities preferred term only and not the composite definition described in the appendix (p 2).

Table 2: **Treatment-related adverse events**

phase who received at least one dose of avelumab or axitinib were analysed for safety and antitimour activity.

Along with proportions of patients with objective responses, we calculated corresponding exact two-sided 95% CIs with the Clopper-Pearson method. Time to tumour response was summarised with descriptive statistics. We assessed antitumour activity in the overall population and in the PD-L1 expression subgroups. Data were analysed with SAS version 9.2. This study is registered with ClinicalTrials.gov, number NCT02493751.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, and data interpretation. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 30, 2015, and Sept 30, 2016, patients were enrolled at 14 sites in the USA, UK, and Japan (appendix p 4). Among 79 patients screened for eligibility, 55 were enrolled. Six were enrolled in the dose-finding phase of the study and 49 were enrolled into the dose-expansion cohort (ten were assigned to a 7 day lead-in with axitinib therapy before the first cycle of combination therapy and 39 started combination therapy directly per protocol; figure 1). Patients' characteristics are summarised in table 1.

Patients in the dose-finding cohort received a median of 32·5 avelumab infusions (IQR 31·0–37·0) during a median follow-up of 69·7 weeks (66·1–74·1). The median duration of treatment was 66·6 weeks (66·0–74·1) with axitinib and 66·0 weeks (65·6–74·0) with avelumab. Among the six patients in the dose-finding cohort, four (67%) had a grade 3 or 4 treatment-related adverse event (grade 3 hypertension, palmar-plantar erythrodysaesthesia, proteinuria, and mucosal inflammation and grade 4 increase in lipase concentration). One patient had a dose-limiting toxicity (grade 3 proteinuria) that led to axitinib dose reduction and resolved without sequelae; this patient continued treatment with avelumab at 10 mg/kg and 3 mg axitinib twice daily. One patient discontinued axitinib due to grade 3 palmar-plantar erythrodysaesthesia syndrome. This patient continued treatment with avelumab monotherapy until disease progression. At the end of the dose-finding phase, the maximum tolerated dose established for the combination was avelumab 10 mg/kg every 2 weeks and axitinib 5 mg twice daily.

We saw no differences in antitumour activity or safety between patients in either phase who received lead-in treatment with axitinib and those who did not. Therefore, we present data for all 55 patients together.

At the cutoff of April 13, 2017, the median follow-up for all 55 patients was 52·1 weeks (IQR 37·4–56·1). 54 (98%) patients received avelumab and axitinib (table 1), and one patient received only axitinib because of an adverse event (grade 3 increase in blood creatine phosphokinase concentration) that arose before avelumab was started. At the time of cutoff, combination treatment was ongoing in 29 (53%) of 55 patients, two (4%) were receiving treatment with axitinib alone, and one (2%) was receiving avelumab alone. Patients received avelumab for a median of 37·0 weeks (IQR 14·0–50·0) and axitinib for a median of 36·0 weeks (18·1–50·1). Reasons for treatment discontinuation were progressive disease (n=11 for avelumab and n=14 for axitinib), adverse events (n=7 for avelumab and n=4 for axitinib), withdrawal of consent (n=3 for both treatments), death (n=2 for both treatments), and physician's decision (n=1 for both treatments).

All 55 patients experienced at least one adverse event during the trial, and 53 (96%) had one or more adverse events that were judged by the investigator to be related to avelumab or axitinib (table 2, appendix p 29). The most frequent treatment-related adverse events (occurring in ≥10% of patients) included diarrhoea, hypertension, dysphonia, fatigue, palmar-plantar erythrodysaesthesia

	All grades	Grade 3	Grade 4	Grade 5
All events	23 (42%)	4 (7%)	0	1 (2%)
Hypothyroidism*	13 (24%)	0	0	0
Rash†	7 (13%)	2 (4%)	0	0
Hepatitis‡	3 (6%)	2 (4%)	0	0
Hyperthyroidism	3 (6%)	0	0	0
Adrenal insufficiency	1 (2%)	0	0	0
Colitis	1 (2%)	1 (2%)	0	0
Myocarditis	1 (2%)	0	0	1 (2%)

Participants who had more than one event within a category are counted only once in that category. All events refers to the number of patients with any immune-related adverse events.*Includes hypothyroidism and increased concentrations of thyroid-stimulating hormone in blood. †Includes rash, pruritus, rash papular, dermatitis acneiform, drug eruption, and rash pustular. ‡Includes increased concentrations of alanine aminotransferase and aspartate aminotransferase.

Table 3: **Immune-related adverse events**

	Dose-finding cohort (n=6)	Dose-expansion cohort (n=49)	All patients (n=55)
Complete response	1 (17%)	2 (4%)	3 (6%)
Partial response	5 (83%)	24 (49%)	29 (53%)
Stable disease	0	11 (22%)	11 (20%)
Progressive disease	0	10 (20%)	10 (18%)
Non-assessable	0	2 (4%)*	2 (4%)*
Objective response	6 (100%, 95% CI 54–100)	26 (53%, 95% CI 38–68)	32 (58%, 95% CI 44–71)
Disease control	6 (100%, 95% CI 54–100)	37 (76%, 95% CI 61–87)	43 (78%, 95% CI 65–88)

Data are number (%) unless stated otherwise. Responses assessed according to Response Evaluation Criteria In Solid Tumors version 1.1. *One patient died from autoimmune myocarditis before the first oncological assessment, and one had the first oncological assessment before the protocol-specified time window then died from disease progression (based on clinical assessment without radiological documentation).

Table 4: **Confirmed best overall responses and objective responses**

syndrome, increased alanine aminotransferase concentration, rash, increased aspartate aminotransferase concentration, hypothyroidism, increased amylase concentration, decreased appetite, mucosal inflammation, infusion-related reactions, increased lipase concentration, and nausea (appendix p 12). 32 (58%) of 55 patients had grade 3 or worse treatment-related adverse events and one died from treatment-related autoimmune myocarditis (confirmed by widespread myocarditis on post-mortem histopathology; viral cause was excluded; tables 2, 3). The onset of grade 3 or worse treatment-related adverse events and their duration during treatment are depicted in the appendix (p 24).

16 (29%) of 55 patients reported infusion-related reactions, most of which were grade 1 or 2; one (2%) patient had a grade 3 infusion-related reaction and discontinued avelumab, and one (2%) additional patient had chills unrelated to treatment. 16 (29%) of 55 patients had infusion-related reactions with the first infusion, and one (2%) had three grade 2 infusion-related reactions at cycles eight, nine, and ten, but continued treatment beyond cycle ten until disease progression.

23 (42%) of 55 patients had immune-related adverse events (table 3); see appendix (p 2) for adjudication criteria. The most frequent was hypothyroidism in 13 (24%) patients, and five (9%) had grade 3 or worse immune-related events, which led to avelumab dose interruption in one patient (due to rash) and discontinuation of avelumab in the other four patients.

20 (36%) of 55 patients had serious adverse events, which were judged to be treatment related in 12 (22%). Serious adverse events occurring in more than one patient were increased alanine aminotransferase concentration (n=2, deemed to be treatment related), infusion-related reactions (n=2 related to avelumab), and presyncope, spinal cord compression, and hypoxia (all n=2, not related to study treatment).

Ten (18%) of 55 patients discontinued one or both study drugs due to adverse events. Seven (13%) of 55 discontinued avelumab, with increased alanine aminotransferase concentration being the only adverse event leading to discontinuation in more than one patient (n=3 [6%]). Four (7%) of 55 patients discontinued axitinib (no events occurred in more than one patient). Six (11%) of 55 patients died before data cutoff: five (9%) due to disease progression (four after the end of treatment) and one (2%) due to treatment-related autoimmune myocarditis.

32 (58%) of 55 patients had avelumab dose delays, with duration of 7 days or longer in 25 (46%) of 55 patients. Four (7%) of 55 patients received less than 90% of the planned avelumab dose in one infusion because of adverse events: three due to infusion-related reactions (one of whom discontinued treatment) and one due to an electrocardiogram abnormality unrelated to study treatment. Axitinib was decreased at least once in 31 (56%) of 55 patients and increased at least once in ten (18%) of 55 patients. Axitinib dose reductions were due to adverse events in 28 (51%) of 55 patients, among whom the most common (in >5% of patients) were palmar-plantar erythrodysaesthesia syndrome (n=6), fatigue (n=5), hypertension (n=4), and proteinuria (n=3).

Objective responses were confirmed in six (100%, 95% CI 54–100) of six patients in the dose-finding cohort and 26 (53%, 38–68) of 49 patients in the dose-expansion

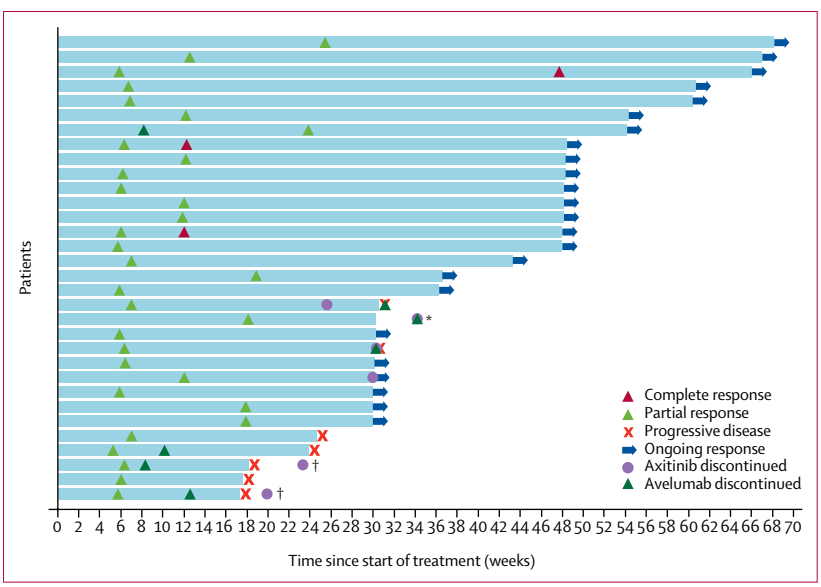

Figure 2: **Durations of confirmed objective responses**
32 patients had confirmed objective responses, as per investigators' assessments. Each bar represents one patient. *Duration of response is censored because the patient withdrew consent (last tumour assessment occurred before the last dose of avelumab and axitinib). †Patients continued treatment after disease progression, as allowed per protocol.

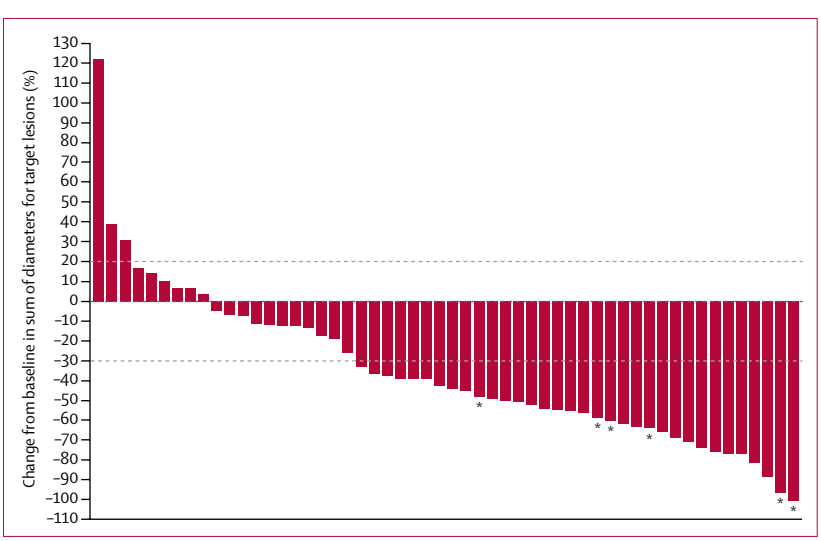

Figure 3: **Change from baseline in sum of diameters for target lesions**
Measurements were available for 54 patients who had target lesions at baseline and at least one target lesion after baseline; one patient who died due to autoimmune myocarditis before the first oncological assessment was not included. One patient had only one oncological assessment after baseline but before the protocol-specified time window and, therefore, was classified as non-assessable but was included in the analysis. This patient had 14% increased tumour burden and subsequently died due to disease progression (based on clinical assessment without radiological documentation). *Patients enrolled in the dose-finding phase.

cohort (32 [58%, 44–71] of 55 in the whole cohort). Three (6%) of 55 patients had complete responses (two of whom had lymph-node target lesions; table 4). Disease control was achieved in 43 (78%) of 55 patients. At the data cutoff date, responses were ongoing in 24 patients (figure 2), with the median duration of response not yet reached. The median time to achieve an objective response was 6·8 weeks (IQR 6·0–12·1). Of 32 objective responses, 20 (69%) were documented at the first tumour assessment (around 6 weeks after starting treatment), six after 12 weeks, and six after 18 weeks or longer. Three complete responses were conversions from partial responses (two at week 12 and one at week 48). Tumour shrinkage was observed in 45 (83%) of 54 patients assessed after baseline (figure 3); the change in the sum of target lesion diameters over time is shown in the appendix (p 25). Duration of response, progression-free survival, and overall survival could not be assessed because data are still immature.

PD-L1 expression could be assessed in tumour samples from 52 patients. In patients who had PD-L1 expression on 1% or more of tumour-associated immune cells, a higher proportion achieved objective responses than those with less than 1% PD-L1 expression on tumour-associated immune cells (table 5). Data for all PD-L1 expression cutoffs on immune cells, tumour cells, and immune and tumour cells combined are summarised in the appendix (p 21). 43 (84%) of 51 patients assessed for PD-L1 status had tumour shrinkage, among whom 33 had shrinkage of 30% or greater. 29 of these 33 patients had PD-L1 expression on 1% or more of tumour-associated immune cells and four patients had PD-L1 expression on less than 1% of tumour-associated immune cells (figure 4).

	Objective response	Odds ratio (95% CI)
1% cutoff		
≥1%	27 (66%, 95% CI 49–80) of 41	3·38 (0·70–18·12)
<1%	4 (36%, 95% CI 11–69) of 11	..
5% cutoff		
≥5%	19 (68%, 95% CI 48–84) of 28	2·11 (0·60–7·57)
<5%	12 (50%, 95% CI 29–71) of 24	..

52 patients had tumour samples assessable for PD-L1 immunohistochemistry. PD-L1=programmed cell death protein ligand.

Table 5: **Objective response by PD-L1 expression on immune cells**

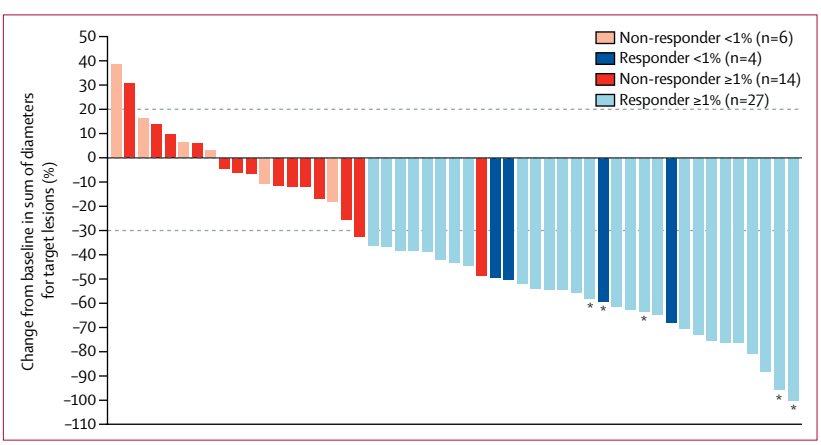

Figure 4: **Change from baseline in sum of diameters in target lesions by PD-L1 expression on tumour-associated immune cells**

Data on PD-L1 expression were available for 51 patients with target lesions at baseline and more than one target lesion after baseline, based on investigator assessment according to Response Evaluation Criteria In Solid Tumors version 1.1; one patient died due to autoimmune myocarditis before the first oncological assessment and was not included, and three patients did not have assessable samples. Patients with complete or partial responses were classified as responders, and those whose best overall response was not a complete or partial response were classified as non-responders. PD-L1=programmed cell death protein ligand. *Patients enrolled in the dose-finding phase.

Discussion

Avelumab combined with axitinib as first-line treatment in patients with advanced renal-cell carcinoma had a manageable safety profile and showed encouraging antitumour activity. The maximum tolerated dose established in the dose-finding phase was avelumab 10 mg/kg every 2 weeks plus axitinib 5 mg twice daily, but further assessment of this dose (ie, clinical feasibility of long-term administration) will inform the recommended phase 2 dose. Although cross-trial comparisons of safety profiles are complicated by differences in study design and reporting (eg, all-cause *vs* treatment-related events), the adverse events observed with combination therapy in this study were largely consistent with the known safety profiles of avelumab[16] and axitinib[23] when used alone or combined with pembrolizumab and axitinib in phase 1/2 studies.[18] No new toxicities were reported. The frequencies of all-grade and grade 3 or 4 events of increased alanine aminotransferase concentrations were slightly higher than those previously reported[23] in a larger set of patients with advanced renal-cell carcinoma treated with axitinib (all grades 29% *vs* 22%; grade 3 or 4 7% [with no grade 4 events] *vs* <1%). The frequencies, types, and severities of immune-related adverse events in this trial were consistent with those reported for other monoclonal antibodies inhibiting PD-L1 and PD-1 interactions,[3] including rare autoimmune myocarditis.[23] Infusion-related reactions were mostly mild to moderate, and occurred mainly at the first infusion. One patient discontinued treatment because of an infusion-related reaction, and the proportion of patients who had axitinib dose reductions was higher than that reported in a previous study of axitinib monotherapy (56% *vs* 25%).[24]

The antitumour activity observed with the combination of avelumab and axitinib was encouraging, with most patients experiencing early and durable responses. The proportion of patients with confirmed objective responses was 58% (95% CI 44–71), which was higher than that seen with axitinib alone, and was consistent with response data from other phase 1/2 studies of monoclonal antibodies inhibiting interactions between PD-L1 and PD-1 combined with angiogenesis inhibitors. For instance, in a study of single-agent axitinib treatment in previously untreated patients with advanced renal-cell

carcinoma, an objective response was seen 62 (32%) of 192 patients.[24] Preliminary results from a phase 1b study of axitinib combined with pembrolizumab as first-line therapy for advanced renal-cell carcinoma showed objective responses in 37 (71%) of 52 patients.[18] In a phase 2 study of bevacizumab combined with atezolizumab compared with sunitinib monotherapy in treatment-naive patients with advanced renal-cell carcinoma, objective responses were seen in 32% and 29% of patients, respectively.[21] Multiple combinations are currently under investigation in phase 3 trials.[3]

In a randomised phase 3 trial that compared the combination of the immune checkpoint inhibitors nivolumab and ipilimumab (a CTLA-4 inhibitor) with sunitinib alone, objective responses were seen in 42% (95% CI 37–47) versus 27% (22–31), and an overall survival improvement was seen with combined therapy for patients in the poor-risk and intermediate-risk categories.[10] The clinical benefit observed in patients with advanced renal cell carcinoma classified into poor-risk and intermediate-risk categories in this study indicates potential for a shift away from single-agent TKIs as preferred first-line standard-of-care treatment.

PD-L1 is often expressed in the tumour microenvironment in patients with renal-cell carcinoma.[25] In our study, PD-L1 expression was assessed on tumour and immune cells, and there seemed to be a correlation between intratumour PD-L1 expression and the likelihood of achieving an objective response after receiving avelumab plus axitinib. Similarly, in the IMmotion 150 trial,[21] the number of patients with objective responses among patients who received bevacizumab and atezolizumab was higher among those with PD-L1 expressed on at least 1% of the tumour-infiltrated immune cells than in those who had PD-L1 expression on less than 1% of the immune infiltrates. In addition, clinical activity in the CheckMate-214 study,[10] which investigated the combination of nivolumab and ipilimumab in patients with renal-cell carcinoma, was substantially higher in patients with tumours positive for PD-L1 than in those without PD-L1 expression. Although in this study we noted an association between objective response and high PD-L1 tumour expression, we did not formally test the predictive value of PD-L1 expression in patients with advanced renal-cell carcinoma treated with avelumab plus axitinib.

This trial had several limitations. It is a single-arm trial with no monotherapy comparator groups, which prevents the direct comparison of the combination treatment with the respective drugs used alone in this population. Additionally, progression-free and overall survival data were not mature at the time of data cutoff because the minimum follow-up time for this analysis was 27·6 weeks and most patients were still receiving treatment. Longer follow-up will aid in further describing the antitumour activity of combined avelumab and axitinib in patients with advanced clear-cell renal-cell carcinoma.

In conclusion, the combination of avelumab and axitinib in treatment-naive patients with advanced renal-cell carcinoma had a manageable safety profile consistent with the profiles of the individual agents when administered as monotherapy, and antitumour activity was encouraging. The JAVELIN Renal 101, randomised, phase 3 trial comparing avelumab and axitinib versus sunitinib monotherapy for first-line treatment of patients with advanced renal-cell carcinoma is ongoing.[26]

Contributors

TKC, MM, TP, PBR, MBA, SG, AC, CF, AdP, and BIR conceived and designed the study. TKC, JL, MM, PN, TP, DM, PBR, DDC, DC, MBA, MSG, SG, HU, YT, AC, AdP, and BIR collected and assembled the data. TKC, JL, MM, PN, DM, PBR, DDC, DC, MBA, MSG, SG, HU, YT, AC, CF, AdP, and BIR analysed and interpreted the data. All authors were involved in writing the Article and approved the final version.

Declaration of interests

TKC has received grants and personal fees from AstraZeneca, Bristol-Myers Squibb, Eisai, Exelixis, GlaxoSmithKline, Merck, Novartis, Pfizer, Peloton, and Roche/Genentech, personal fees from Bayer, Cerulean, Corvus, Foundation Medicine, and Prometheus Laboratories, and grants from Tracon. JL has received grants and personal fees from Bristol-Myers Squibb, Merck, Novartis, and Pfizer, personal fees from Eisai, EUSA Pharma, GlaxoSmithKline, Kymab, Pierre Fabre, Roche/Genentech, and Secarna. MO has received grants and personal fees from Asahi Kasei Pharma, Astellas Pharma, Novartis Pharma, Ono Pharmaceutical, and Pfizer Japan, grants from ASKA Pharmaceutical, and personal fees from AstraZeneca, Bayer Yakuhin, Boston Scientific Corp, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Hisamitsu Pharmaceutical, Janssen Pharmaceutical, Meiji Seika Pharma, Merck, Nihon Medi-Physics, Nippon Kayaku, Nippon Shinyaku, Kissei Pharmaceutical, Kyorin Pharmaceutical, Kyowa Hakko Kirin, Sanofi, Shionogi, Sumitomo Dainippon Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Teijin Pharma, and Tsumura. FT has received grants from Bristol-Myers Squibb and Novartis. MM, AC, CF, and AdP are employees of Pfizer. MM and AdP have a pending patent (WO2016205277). PN has received personal fees from Merck. TP has received personal fees from AstraZeneca, Merck, Novartis, Pfizer, and Roche, and grants from AstraZeneca and Roche. DM has received personal fees from Array BioPharm, Bristol-Myers Squibb, Eisai, Exelixis, Genentech BioOncology, Merck, Novartis, and Pfizer, and grants from Prometheus Laboratories. PBR was an employee of Pfizer during the trial, has been an employee of AstraZeneca, and has pending patents (anti-PD-L1 and anti-CTLA-4 antibodies for treating solid tumours; anti-B7-H1 antibodies for treating tumours; and antibodies and methods of detection of an immune modulator). DDC has received personal fees from Exelixis and Karyopharm. DC has received personal fees from Bristol-Myers Squibb, Exelixis, Genentech, Pfizer, and Prometheus Laboratories. MBA has received grants and personal fees from Pfizer and personal fees from Bristol-Myers Squibb, Exelixis, Eisai, Merck, Novartis, and Roche. SG's institution received funding from Bristol-Myers Squibb, Five Prime, Hoosier, Incyte, Merck, Novartis, Pfizer, Rexahn, and Viralytics, and SG's spouse holds stock in Salarius. YT has received grants from Astellas, AstraZeneca, Bristol-Myers Squibb, Ono Pharmaceutical, Pfizer, and personal fees from Astellas, AstraZeneca, Ono Pharmaceutical, and Pfizer. BIR has received grants and personal fees from Pfizer. The other authors declare no competing interests.

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