





ORIGINAL ARTICLE

Avelumab plus axitinib vs sunitinib for advanced renal cell carcinoma: Japanese subgroup analysis from JAVELIN Renal 101

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Abstract

The phase 3 JAVELIN Renal 101 trial of avelumab + axitinib vs sunitinib in patients with treatment-naïve advanced renal cell carcinoma (RCC) demonstrated significantly improved progression-free survival (PFS) and higher objective response rate (ORR) with the combination vs sunitinib. Japanese patients enrolled in the study (N = 67) were randomized to receive avelumab + axitinib (N = 33) or sunitinib (N = 34); 67% vs 59% had PD-L1+ tumors ($\geq 1\%$ of immune cells) and 6%/64%/27% vs 6%/82%/12% had International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favorable/intermediate/poor risk status. In patients who received avelumab + axitinib vs sunitinib, median PFS (95% confidence interval [CI]) was not estimable (8.1 months, not estimable) vs 11.2 months (1.6 months, not estimable) (hazard ratio [HR], 0.49; 95% CI, 0.152, 1.563) in patients with PD-L1+ tumors and 16.6 months (8.1 months, not estimable) vs 11.2 months (4.2 months, not estimable) (HR, 0.66; 95% CI, 0.296, 1.464) in patients irrespective of PD-L1 expression. Median overall survival (OS) has not been reached in either arm in patients with PD-L1+ tumors and irrespective of PD-L1 expression. ORR (95% CI) was 60.6% (42.1%, 77.1%) vs 17.6% (6.8%, 34.5%) in patients irrespective of PD-L1 expression. Common treatment-emergent adverse events (all grade; grade ≥ 3) in each arm were hand-foot syndrome (64%; 9% vs 71%; 9%), hypertension (55%; 30% vs 44%; 18%), hypothyroidism (55%; 0% vs 24%; 0%), dysgeusia (21%; 0% vs 56%; 0%) and platelet count decreased (3%; 0% vs 65%; 32%). Avelumab + axitinib was efficacious and tolerable in treatment-naïve Japanese patients with advanced RCC, which is consistent with results in the overall population.

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avelumab, axitinib, Japan, phase 3 JAVELIN Renal 101 clinical trial, renal cell carcinoma

1 | INTRODUCTION

Approximately 70% of patients who are diagnosed with renal cell carcinoma (RCC), the most common type of kidney cancer, have predominantly clear-cell histology, which is associated with genetic mutations that promote tumor angiogenesis through increased production of vascular endothelial growth factor (VEGF).^{1,2} This fundamental finding prompted the development, investigation and approval of several targeted therapies that either block VEGF from binding to its cognate receptors, VEGFR, or impair the intrinsic kinase activity of VEGFR.¹ Sunitinib, a VEGFR tyrosine kinase inhibitor, is a recommended first-line therapy for patients with locally advanced or metastatic clear-cell RCC, which accounts for approximately 30% of diagnoses of RCC.^{3,4} Despite the availability of multiple antiangiogenic therapies to treat advanced RCC, most patients will eventually develop progressive disease and the 5-year survival rate for these patients is approximately 10%.² Accordingly, there is an unmet medical need for novel, more efficacious therapies to treat this fatal disease.

Avelumab, a human anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitory monoclonal antibody, has shown acceptable safety and durable antitumor activity in multiple tumor types, including RCC,⁵⁻⁹ and has been approved in several countries as monotherapy for the treatment of metastatic Merkel cell carcinoma as well as in the United States and Canada for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed on platinum-containing chemotherapy. Avelumab showed a manageable safety profile in Japanese patients with advanced solid tumors and clinical activity in patients with advanced gastric cancer/gastroesophageal junction cancer that had progressed after chemotherapy in the phase 1 JAVELIN Solid Tumor JPN trial.¹⁰ Avelumab was also approved for curatively unresectable Merkel cell carcinoma in Japan in September 2017.

Axitinib is a potent and selective inhibitor of VEGFR-1, 2 and 3 and has shown antitumor activity as a single agent with an acceptable safety profile. The randomized phase 3 AXIS trial demonstrated a significant improvement in progression-free survival (PFS) with axitinib over sorafenib.^{11,12} Axitinib has been approved for the second-line treatment of advanced RCC. Second-line treatment with axitinib was

well tolerated and showed antitumor activity in Japanese patients with metastatic RCC¹³⁻¹⁵ and was approved for second-line treatment of advanced RCC in Japan in June 2012. Axitinib has also shown antitumor activity and a manageable safety profile for the treatment of patients with metastatic RCC in the first-line setting in randomized studies,^{16,17} including in Japanese patients.^{18,19}

Axitinib also has immunomodulatory effects that can enhance tumor infiltration of immune cells and impair immune suppressor cells.²⁰ Simultaneous inhibition of the programmed death-1 (PD-1)/PD-L1 immune checkpoint and VEGF/VEGFR signaling showed synergistic antitumor effects in preclinical models,²¹ leading to the hypothesis that treatment with a combination of these two drug classes might have clinical benefit above that of either drug alone. Preliminary data from a single-arm phase 1b study of avelumab + axitinib in treatment-naïve patients with advanced RCC showed a manageable safety profile and encouraging antitumor activity, with an objective response rate (ORR) of 58%.²² The randomized phase 3 JAVELIN Renal 101 clinical trial of avelumab + axitinib vs sunitinib in previously untreated patients with advanced RCC demonstrated longer PFS (median, 13.8 vs 7.2 months; stratified hazard ratio [HR], 0.61; $P < 0.001$) and higher ORR (55.2% vs 25.5%) with the combination vs sunitinib in patients with PD-L1+ tumors.²³ PFS and ORR benefits were also observed in patients irrespective of PD-L1 expression. The median PFS was 13.8 vs 8.4 months (stratified HR, 0.69; $P < 0.001$) and ORR was 51.4% vs 25.7%, respectively. Median overall survival (OS) had not been reached in either arm in either population. Based on the results from JAVELIN Renal 101, the combination of avelumab + axitinib was approved in the United States and European Union for the first-line treatment of patients with advanced RCC.

Different intrinsic demographic factors, such as genetic background, dietary habits, and medical environments (eg, diagnostic surveillance and available treatment options) may influence clinical outcomes.²⁴⁻²⁶ Therefore, it is critical to evaluate efficacy and safety in different ethnic populations. The aim of the current analysis was to evaluate the efficacy and safety of avelumab + axitinib compared with sunitinib in Japanese patients enrolled in the JAVELIN Renal 101 clinical trial.

2 | PATIENTS AND METHODS

2.1 | Study design, patients and treatment

The study design and patient eligibility criteria have been described in detail previously.²³ This was a multicenter, randomized, open-label, phase 3 trial comparing avelumab + axitinib with sunitinib. Randomization (1:1) was stratified according to Eastern Cooperative Oncology Group performance status (ECOG PS) score (0 vs 1) and geographic region (United States vs Canada and Western Europe vs the rest of the world). Eligible patients were aged ≥ 18 years (≥ 20 years in Japan) with previously untreated advanced RCC with a clear-cell component. Additional inclusion criteria included the presence of ≥ 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; ECOG PS score of 0 or 1; a fresh or archival tumor specimen; and adequate renal, cardiac and hepatic function. Patients across all Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk groups were included.

Avelumab was administered at a dose of 10 mg/kg as a 1-hour intravenous infusion every 2 weeks. An antihistamine and acetaminophen were administered approximately 30-60 minutes before each infusion. Axitinib was administered orally at a starting dose of 5 mg twice daily on a continuous dosing schedule. Sunitinib was administered at a dose of 50 mg orally once daily for 4 weeks of a 6-week cycle. Dose escalations and reductions of axitinib and dose reductions of sunitinib are described in the protocol and in the respective package inserts. Dose reductions of avelumab were not permitted, but subsequent infusions could be omitted in response to persisting toxic effects.

The two independent primary end points were PFS as determined by blinded independent central review (BICR) according to RECIST 1.1 and OS among patients with PD-L1+ tumors ($\geq 1\%$ of immune cells staining positive within the tumor area of the tested tissue sample). PD-L1 expression was assessed at a central laboratory with the use of the Ventana PD-L1 (SP263) assay (Ventana Medical Systems). Key secondary end points were PFS as determined by BICR according to RECIST 1.1 and OS among patients in the overall population, irrespective of PD-L1 expression. Other secondary end points included investigator-assessed PFS, ORR, adverse events, pharmacokinetic measures, tumor tissue biomarkers and patient-reported outcomes.

The trial was conducted in accordance with the ethics principles of the Declaration of Helsinki and the Good Clinical Practice guidelines, defined by the International Council for Harmonisation. All patients provided written informed consent. The protocol, amendments and informed-consent forms were approved by the institutional review board or independent ethics committee at each trial site. An independent external data monitoring committee reviewed efficacy and safety.

2.2 | Assessments

Tumors were assessed using computed tomography or magnetic resonance imaging at baseline, every 6 weeks after randomization

for the first 18 months, and then every 12 weeks until confirmed disease progression. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Patients in each treatment group were permitted to continue therapy after RECIST-defined disease progression if the investigators determined that the therapy had benefit (eg, patients did not have clinical signs and symptoms associated with the radiographic findings).

2.3 | Statistical analysis

Calculation of the overall sample size required for the primary and key secondary endpoints, the statistical testing schemes and the preplanned interim analysis have been described previously.²³ Results are reported per the data cutoff for the first interim analysis. Efficacy end points were assessed in all patients who underwent randomization, and safety was evaluated in all patients who received ≥ 1 dose of a trial drug. PFS and OS were estimated using the Kaplan-Meier method, and one-sided *P*-values using the log-rank test were reported. The 95% CI for the HR was determined. The ORR was calculated according to treatment group along with corresponding exact one-sided 95% CI using the Clopper-Pearson method. The stratified odds ratio and its CI were estimated using the Mantel-Haenszel method.

3 | RESULTS

3.1 | Baseline characteristics and patient disposition

Details of the patients enrolled in the JAVELIN Renal 101 clinical trial have been described previously.²³ Briefly, 886 patients were randomized at 144 study sites in 21 countries between March 29, 2016, and December 19, 2017. A total of 442 patients were randomized to receive avelumab + axitinib and 444 to receive sunitinib, including 33 and 34 Japanese patients, respectively. Baseline demographic and disease characteristics in the PD-L1+ group and in patients irrespective of PD-L1 expression are shown in Tables 1 and 2. As in the overall population, most Japanese patients were male with intermediate MSKCC or IMDC prognostic risk criteria and stage IV disease in both the combination arm and the sunitinib arm. Among Japanese patients, a higher percentage of women or patients with poor MSKCC or IMDC prognostic risk criteria were randomized to the combination arm than in the sunitinib arm in both the PD-L1+ group and in patients irrespective of PD-L1 expression. Compared with the overall population, Japanese patients had a lower median weight, a smaller proportion of patients with MSKCC/IMDC favorable prognostic risk, a higher proportion of patients with stage IV disease at diagnosis, and shorter time from histopathological diagnosis to randomization. As of June 20, 2018 (data cutoff date), of the 33 Japanese patients randomized to the combination arm, 19 (57.6%) were still receiving avelumab

TABLE 1 Baseline demographic and clinical characteristics of patients with PD-L1+ tumors

Characteristic	PD-L1+ group: Overall population (N = 560)		PD-L1+ group: Japanese patients (N = 42)	
	Avelumab + axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + axitinib (N = 22)	Sunitinib (N = 20)
Age, median (range), y	62.0 (29.0, 83.0)	60.5 (27.0, 88.0)	63.5 (43.0, 73.0)	66.5 (38.0, 78.0)
Sex, n (%)				
Male	203 (75.2)	224 (77.2)	17 (77.3)	18 (90.0)
Female	67 (24.8)	66 (22.8)	5 (22.7)	2 (10.0)
Weight, median (range), kg	80.8 (44.2, 143.3)	82.3 (41.4, 176.4)	63.9 (44.2, 79.2)	69.3 (41.4, 90.5)
Race, n (%)				
Black or African American	8 (3.0)	5 (1.7)	0	0
American Indian or Alaska native	3 (1.1)	4 (1.4)	0	0
Asian	40 (14.8)	41 (14.1)	22 (100.0)	20 (100.0)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	201 (74.4)	225 (77.6)	0	0
Other	7 (2.6)	5 (1.7)	0	0
Unknown	11 (4.1)	10 (3.4)	0	0
ECOG PS score, n (%)				
0	174 (64.4)	193 (66.6)	15 (68.2)	16 (80.0)
1	96 (35.6)	96 (33.1)	7 (31.8)	4 (20.0)
2	0	1 (0.3)	0	0
Not reported	0	0	0	0
MSKCC prognostic risk, n (%)				
Favorable	52 (19.3)	60 (20.7)	0	1 (5.0)
Intermediate	180 (66.7)	201 (69.3)	18 (81.8)	18 (90.0)
Poor	33 (12.2)	24 (8.3)	4 (18.2)	1 (5.0)
Not reported	5 (1.9)	5 (1.7)	0	0
IMDC prognostic risk, n (%)				
Favorable	52 (19.3)	59 (20.3)	0	1 (5.0)
Intermediate	173 (64.1)	191 (65.9)	17 (77.3)	19 (95.0)
Poor	44 (16.3)	39 (13.4)	5 (22.7)	0
Not reported	1 (0.4)	1 (0.3)	0	0
Previous nephrectomy, n (%)				
Yes	233 (86.3)	252 (86.9)	17 (77.3)	17 (85.0)
No	37 (13.7)	38 (13.1)	5 (22.7)	3 (15.0)
TNM stage at initial diagnosis, n (%)				
I	24 (8.9)	23 (7.9)	2 (9.1)	2 (10.0)
IA	0	1 (0.3)	0	0
IB	3 (1.1)	5 (1.7)	0	1 (5.0)
II	21 (7.8)	27 (9.3)	1 (4.5)	2 (10.0)
IIA	5 (1.9)	2 (0.7)	0	0
IIB	1 (0.4)	1 (0.3)	0	0
III	61 (22.6)	48 (16.6)	2 (9.1)	2 (10.0)
IIIA	16 (5.9)	14 (4.8)	0	0
IIIB	3 (1.1)	3 (1.0)	0	0
IV	116 (43.0)	135 (46.6)	15 (68.2)	11 (55.0)

(Continues)

TABLE 1 (Continued)

Characteristic	PD-L1+ group: Overall population (N = 560)		PD-L1+ group: Japanese patients (N = 42)	
	Avelumab + axitinib	Sunitinib	Avelumab + axitinib	Sunitinib
	(N = 270)	(N = 290)	(N = 22)	(N = 20)
IVA	4 (1.5)	4 (1.4)	0	0
IVB	2 (0.7)	1 (0.3)	0	1 (5.0)
IVC	1 (0.4)	0	0	0
IV M1A	5 (1.9)	9 (3.1)	0	0
IV M1B	2 (0.7)	3 (1.0)	2 (9.1)	1 (5.0)
IV M1C	0	3 (1.0)	0	0
Unknown	4 (1.5)	9 (3.1)	0	0
Not reported	2 (0.7)	2 (0.7)	0	0
Time from histopathological diagnosis to randomization, median (range), months	6.4 (0.5, 293.0)	5.2 (0.3, 268.1)	2.1 (0.7, 109.2)	3.2 (0.9, 103.0)
Time from recurrence/metastatic disease to randomization, median (range), months	2.2 (0.1, 193.0)	2.3 (0.0, 75.0)	1.8 (0.7, 75.3)	1.8 (0.6, 7.2)
RECIST-defined number of target tumor sites at baseline per independent review, n (%)				
0	8 (3.0)	11 (3.8)	1 (4.5)	2 (10.0)
1	120 (44.4)	118 (40.7)	12 (54.5)	9 (45.0)
2	85 (31.5)	101 (34.8)	7 (31.8)	8 (40.0)
3	40 (14.8)	50 (17.2)	2 (9.1)	0
≥4	17 (6.3)	10 (3.4)	0	1 (5.0)

Note: Data for overall population are from reference²³. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TNM, tumor, node, metastasis.

and 21 (63.6%) were still receiving axitinib, 19 (57.6%) continued to receive combination therapy, none were receiving avelumab alone, and 2 (6.1%) continued to receive axitinib alone. Of the 34 Japanese patients randomized to the sunitinib arm, 15 (44.1%) remained on treatment. The most common reason for treatment discontinuation was disease progression (avelumab, n = 7 [21.2%]; axitinib, n = 9 [27.3%]; sunitinib, n = 12 [35.3%]) followed by adverse event (avelumab, n = 6 [18.2%]; axitinib, n = 1 [3.0%]; sunitinib, n = 5 [14.7%]).

3.2 | Efficacy

Among the overall population in the PD-L1+ group, median PFS was significantly longer with avelumab + axitinib than with sunitinib: 13.8 months (95% CI, 11.1 months, not estimable) vs 7.2 months (95% CI, 5.7, 9.7 months), respectively (stratified HR, 0.61; 95% CI, 0.475, 0.790; $P < 0.001$) (Figure 1A).²³ The median follow up for PFS was 9.9 vs 8.4 months, respectively. Among Japanese patients in the PD-L1+ group, median PFS in the avelumab + axitinib arm was not estimable (95% CI, 8.1 months, not estimable) vs 11.2 months (95% CI, 1.6 months, not estimable) in the sunitinib arm (stratified HR, 0.49; 95% CI, 0.152, 1.563) (Figure 1B).

The median follow up for PFS was 9.7 vs 14.0 months, respectively. Among Japanese patients, deaths from any cause were observed in 1 patient (4.5%) who received the combination and 2 patients (10.0%) who received sunitinib. OS was immature at the time of data cutoff: median OS was not estimable for either arm (stratified HR, 0.53; 95% CI, 0.042, 6.693). Median follow up for OS was 9.9 vs 12.9 months, respectively.

Among the overall population irrespective of PD-L1 expression, median PFS was significantly longer with avelumab + axitinib than with sunitinib: 13.8 months (95% CI, 11.1 months, not estimable) vs 8.4 months (95% CI, 6.9, 11.1 months), respectively (stratified HR, 0.69; 95% CI, 0.563, 0.840; $P < 0.001$) (Figure 1C).²³ Median follow up for PFS was 10.8 vs 8.6 months, respectively. Among Japanese patients irrespective of PD-L1 expression, median PFS in the avelumab + axitinib arm was 16.6 months (95% CI, 8.1 months, not estimable) vs 11.2 months (95% CI, 4.2 months, not estimable) in the sunitinib arm (stratified HR, 0.66; 95% CI, 0.296, 1.464) (Figure 1D). Median follow up for PFS was 9.8 vs 12.5 months, respectively. Among Japanese patients, deaths from any cause were observed in 3 patients (9.1%) who received the combination and 6 patients (17.6%) who received sunitinib. OS was immature at the time of data cutoff: median OS was not estimable for either arm (stratified HR, 0.42;

TABLE 2 Baseline demographic and clinical characteristics of patients irrespective of PD-L1 expression

Characteristic	Overall population (N = 886)		Japanese patients (N = 67)	
	Avelumab + axitinib (N = 442)	Sunitinib (N = 444)	Avelumab + axitinib (N = 33)	Sunitinib (N = 34)
Age, median (range), y	62.0 (29.0, 83.0)	61.0 (27.0, 88.0)	64.0 (43.0, 81.0)	65.0 (38.0, 85.0)
Sex, n (%)				
Male	316 (71.5)	344 (77.5)	23 (69.7)	29 (85.3)
Female	126 (28.5)	100 (22.5)	10 (30.3)	5 (14.7)
Weight, median (range), kg	81.0 (44.2, 143.3)	82.0 (41.4, 193.1)	60.3 (44.2, 79.2)	67.9 (41.4, 90.5)
Race, n (%)				
Black or African American	10 (2.3)	10 (2.3)	0	0
American Indian or Alaska native	4 (0.9)	4 (0.9)	0	0
Asian	70 (15.8)	63 (14.2)	33 (100.0)	34 (100.0)
Native Hawaiian or other Pacific Islander	0	1 (0.2)	0	0
White	332 (75.1)	334 (75.2)	0	0
Other	9 (2.0)	14 (3.2)	0	0
Unknown	17 (3.8)	18 (4.1)	0	0
ECOG PS score, n (%)				
0	284 (64.3)	276 (62.2)	25 (75.8)	27 (79.4)
1	157 (35.5)	167 (37.6)	8 (24.2)	7 (20.6)
2	0	1 (0.2)	0	0
Not reported	1 (0.2)	0	0	0
MSKCC prognostic risk, n (%)				
Favorable	96 (21.7)	100 (22.5)	2 (6.1)	2 (5.9)
Intermediate	283 (64.0)	293 (66.0)	23 (69.7)	29 (85.3)
Poor	51 (11.5)	45 (10.1)	7 (21.2)	3 (8.8)
Not reported	12 (2.7)	6 (1.4)	1 (3.0)	0
IMDC prognostic risk, n (%)				
Favorable	94 (21.3)	96 (21.6)	2 (6.1)	2 (5.9)
Intermediate	271 (61.3)	276 (62.2)	21 (63.6)	28 (82.4)
Poor	72 (16.3)	71 (16.0)	9 (27.3)	4 (11.8)
Not reported	5 (1.1)	1 (0.2)	1 (3.0)	0
Previous nephrectomy, n (%)				
Yes	352 (79.6)	355 (80.0)	22 (66.7)	23 (67.6)
No	90 (20.4)	89 (20.0)	11 (33.3)	11 (32.4)
TNM stage at initial diagnosis, n (%)				
I	35 (7.9)	36 (8.1)	4 (12.1)	3 (8.8)
IA	1 (0.2)	1 (0.2)	0	0
IB	10 (2.3)	10 (2.3)	0	2 (5.9)
II	39 (8.8)	39 (8.8)	2 (6.1)	2 (5.9)
IIA	8 (1.8)	5 (1.1)	0	1 (2.9)
IIB	4 (0.9)	2 (0.5)	0	0
III	93 (21.0)	71 (16.0)	2 (6.1)	2 (5.9)
IIIA	25 (5.7)	20 (4.5)	0	0
IIIB	6 (1.4)	6 (1.4)	0	0
IV	184 (41.6)	202 (45.5)	21 (63.6)	22 (64.7)
IVA	4 (0.9)	6 (1.4)	0	0

(Continues)

TABLE 2 (Continued)

Characteristic	Overall population (N = 886)		Japanese patients (N = 67)	
	Avelumab + axitinib (N = 442)	Sunitinib (N = 444)	Avelumab + axitinib (N = 33)	Sunitinib (N = 34)
IVB	3 (0.7)	1 (0.2)	1 (3.0)	1 (2.9)
IVC	1 (0.2)	2 (0.5)	0	0
IV M1A	12 (2.7)	11 (2.5)	0	0
IV M1B	2 (0.5)	3 (0.7)	2 (6.1)	1 (2.9)
IV M1C	2 (0.5)	5 (1.1)	0	0
Unknown	9 (2.0)	18 (4.1)	1 (3.0)	0
Not reported	4 (0.9)	6 (1.4)	0	0
Time from histopathological diagnosis to randomization, median (range), months	7.2 (0.4, 428.9)	5.2 (0.2, 354.0)	2.1 (0.7, 166.0)	2.0 (0.7, 103.0)
Time from recurrence/metastatic disease to randomization, median (range), months	2.3 (0.1, 243.9)	2.3 (0.0, 75.0)	2.0 (0.7, 75.3)	1.8 (0.6, 39.6)
RECIST-defined number of target tumor sites at baseline per independent review, n (%)				
0	11 (2.5)	16 (3.6)	1 (3.0)	2 (5.9)
1	181 (41.0)	174 (39.2)	16 (48.5)	14 (41.2)
2	148 (33.5)	151 (34.0)	13 (39.4)	13 (38.2)
3	67 (15.2)	79 (17.8)	2 (6.1)	2 (5.9)
≥4	35 (7.9)	24 (5.4)	1 (3.0)	3 (8.8)

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Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TNM, tumor, node, metastasis.

95% CI, 0.102, 1.729) (Figure S1). Median follow up for OS was 11.1 vs 12.9 months, respectively.

Among the overall population in the PD-L1+ group, the confirmed ORR was 55.2% (95% CI, 49.0%, 61.2%) with avelumab + axitinib vs 25.5% (95% CI, 20.6%, 30.9%) with sunitinib; confirmed complete response rates were 4.4% vs 2.1%, respectively (Table 3).²³ Among Japanese patients in the PD-L1+ group, the confirmed ORR was 68.2% (95% CI, 45.1%, 86.1%) with avelumab + axitinib vs 15.0% (95% CI, 3.2%, 37.9%) with sunitinib; no patient in the combination arm achieved complete response, whereas 1 patient (5.0%) who received sunitinib had a confirmed complete response (Table 3). The median time to response with avelumab + axitinib was 1.6 months (range, 1.3, 4.2 months), with responses ongoing in 11 patients (73.3%) (Table 3).

Similar results were observed in the overall population and in Japanese patients irrespective of PD-L1 status. In the overall population irrespective of PD-L1 expression, the confirmed ORR was 51.4% (95% CI, 46.6%, 56.1%) with avelumab + axitinib vs 25.7% (95% CI, 21.7%, 30.0%) with sunitinib; confirmed complete response rates were 3.4% vs 1.8%, respectively (Table 4).²³ Among Japanese patients irrespective of PD-L1 expression, the confirmed ORR was 60.6% (95% CI, 42.1%, 77.1%) with avelumab + axitinib vs 17.6% (95% CI, 6.8%, 34.5%) with sunitinib; no patient in the combination arm achieved complete response, whereas 1 patient (2.9%) who received sunitinib had a confirmed complete response

(Table 4). The median time to response with avelumab + axitinib was 2.8 months (range, 1.3, 5.6 months), with responses ongoing in 12 patients (60%) (Table 4). The time to and duration of response to avelumab + axitinib in all Japanese patients based on BICR are shown in Figure 2. The change in the sum of target lesion diameters in all Japanese patients according to BICR is shown in Figures 3 and 4.

Efficacy results in Japanese patients according to investigator assessment were consistent with those per BICR and in the overall population²³; in Japanese patients, median PFS was not estimable vs 11.2 months (stratified HR, 0.53) and 12.6 vs 11.1 months (stratified HR, 0.64) in the respective arms of the PD-L1+ group and in patients irrespective of PD-L1 expression, and the ORR were 68.2% (95% CI, 45.1%, 86.1%) vs 35.0% (95% CI, 15.4%, 59.2%) and 57.6% (95% CI, 39.2%, 74.5%) vs 38.2% (95% CI, 22.2%, 56.4%) in the respective arms of the PD-L1+ group and in patients irrespective of PD-L1 expression (Figure S2 and Tables S1 and S2).

3.3 | Exposure

Among all Japanese patients, the median duration of treatment was 7.8 months (range, 0.5, 23.0 months) with avelumab, 8.7 months (range, 0.6, 22.8 months) with axitinib and 8.4 months (range, 0.5, 23.0 months) with sunitinib, which are comparable to those in the

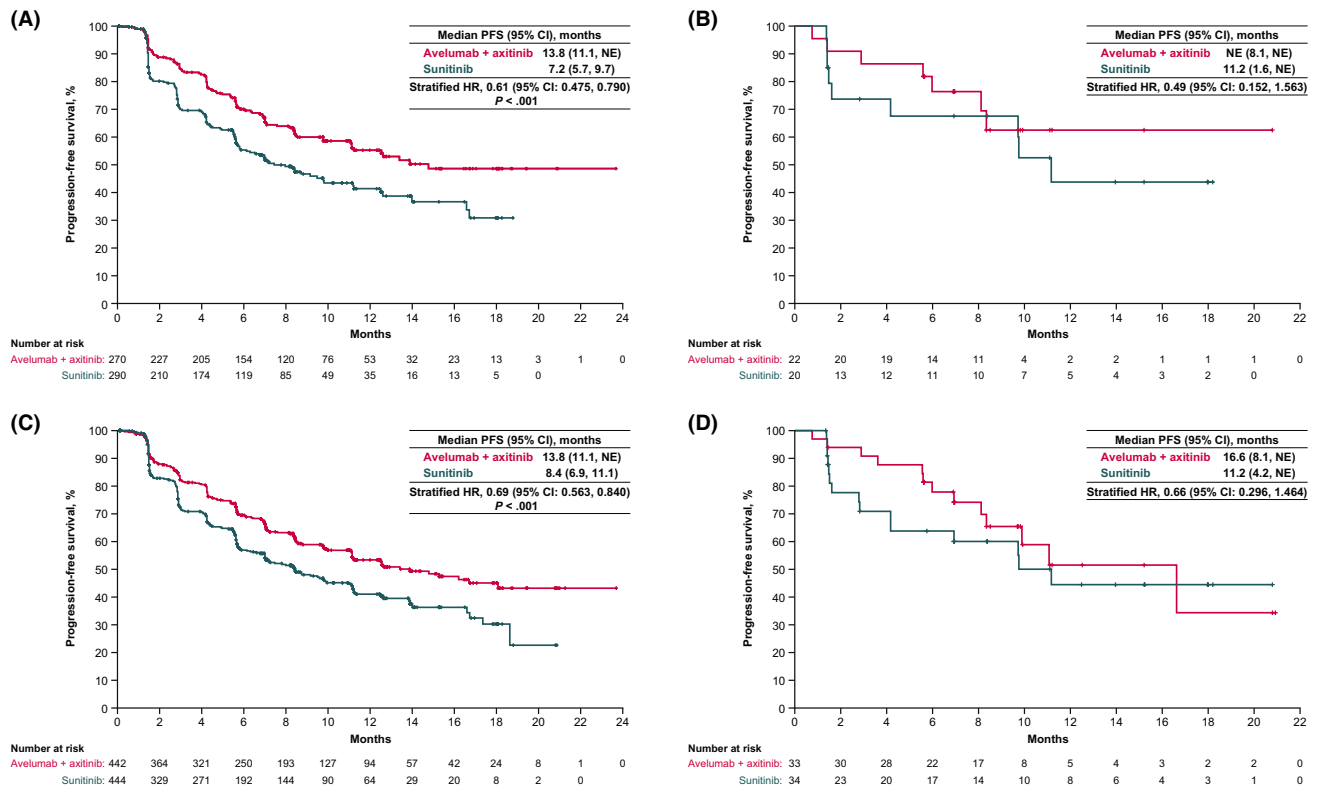


FIGURE 1 PFS per BICR in patients with PD-L1+ tumors in the overall population (A) and Japanese patients (B) and in patients irrespective of PD-L1 expression in the overall population (C) and Japanese patients (D). BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PD-L1, programmed death-ligand 1; PFS, progression-free survival. Data for overall population are from reference 23.

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overall population (Table 5). Among patients who received axitinib in the combination arm, 23 (69.7%) Japanese patients had at least one axitinib dose reduction compared with 183 patients (42.2%) in the overall population. Of patients who received sunitinib, 25 (73.5%) Japanese patients had at least one sunitinib dose reduction compared with 187 (42.6%) patients in the overall population. One Japanese patient (3.0%) had axitinib dose increase compared with 47 patients (10.8%) in the overall population. The median relative dose intensity was 89.8%, 69.4% and 55.5% among Japanese patients who received avelumab, axitinib and sunitinib, respectively, compared with 91.5%, 89.4% and 83.9%, respectively, in the overall population.

3.4 | Safety

Among all Japanese patients, treatment-emergent adverse events of any grade occurred in 33 of 33 patients (100.0%) treated with avelumab + axitinib and 34 of 34 patients (100.0%) treated with sunitinib; grade ≥ 3 treatment-emergent adverse events occurred in 21 patients (63.6%) and 29 patients (85.3%) in the respective groups (Table 6). Diarrhea, hypertension and hand-foot syndrome were the most common ($\geq 40\%$) treatment-emergent adverse events in both the combination arm and the sunitinib arm among Japanese patients. Dysphonia, hypothyroidism and

infusion-related reaction were more frequently ($>20\%$ difference) reported in the combination arm, whereas dysgeusia, pyrexia, anemia, malaise, platelet count decreased, white blood cell count decreased and neutrophil count decreased were more frequently reported in the sunitinib arm among Japanese patients. The incidences of any-grade hand-foot syndrome and hypothyroidism were higher ($>20\%$ difference) in Japanese patients than in patients in the overall population who received the combination. The incidences of grade ≥ 3 events of alanine aminotransferase increased, γ -glutamyltransferase increased, hyperthyroidism and hepatic function abnormal were higher ($>5\%$ difference) in Japanese patients than in patients in the overall population who received the combination.

In the overall population, treatment-emergent adverse events led to discontinuation of avelumab in 84 patients (19.4%), axitinib in 56 patients (12.9%), and both avelumab and axitinib in 33 patients (7.6%), and led to discontinuation of sunitinib in 59 patients (13.4%). The most common treatment-emergent adverse events (occurring in ≥ 4 patients) that led to discontinuation of avelumab were alanine aminotransferase increased ($n = 15$ [3.5%]), aspartate aminotransferase increased ($n = 10$ [2.3%]) and infusion-related reaction ($n = 8$ [1.8%]); those that led to discontinuation of axitinib were alanine aminotransferase increased ($n = 5$ [1.2%]) and aspartate aminotransferase increased ($n = 4$ [0.9%]). Hand-foot

TABLE 3 Antitumor activity per BICR in patients with PD-L1+ tumors

Characteristic	PD-L1+ group: Overall population (N = 560)		PD-L1+ group: Japanese patients (N = 42)	
	Avelumab + axitinib (N = 270)	Sunitinib (N = 290)	Avelumab + axitinib (N = 22)	Sunitinib (N = 20)
Confirmed objective response rate (95% CI), %	55.2 (49.0, 61.2)	25.5 (20.6, 30.9)	68.2 (45.1, 86.1)	15.0 (3.2, 37.9)
Stratified odds ratio (95% CI) ^a	3.73 (2.532, 5.371)		10.78 (2.125, 71.865)	
Confirmed best overall response, n (%)				
Complete response	12 (4.4)	6 (2.1)	0	1 (5.0)
Partial response	137 (50.7)	68 (23.4)	15 (68.2)	2 (10.0)
Stable disease	72 (26.7)	125 (43.1)	4 (18.2)	10 (50.0)
Progressive disease	30 (11.1)	63 (21.7)	2 (9.1)	5 (25.0)
Not evaluable	12 (4.4) ^b	21 (7.2) ^c	0	0
Other ^d	7 (2.6)	7 (2.4)	1 (4.5)	2 (10.0)
Median time to response (range), months	1.6 (1.2, 10.1)	3.0 (1.2, 11.6)	1.6 (1.3, 4.2)	1.4 (1.4, 2.8)
Patients with ongoing response, n/total n (%)	108/149 (72.5)	48/74 (64.9)	11/15 (73.3)	3/3 (100.0)

Note: Data for overall population are from reference 23. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; PD-L1, programmed death-ligand 1.

^aOdds ratio >1 indicates better outcome with avelumab + axitinib compared to sunitinib.

^bNo postbaseline assessments due to early death or other reasons such as withdrawal of consent (n = 10); stable disease <6 wk after randomization (n = 2).

^cNo postbaseline assessments due to early death or other reasons such as withdrawal of consent (n = 9); stable disease <6 wk after randomization (n = 9); new anticancer therapy started before first postbaseline assessment (n = 2); all postbaseline assessments have overall response of not evaluable (n = 1).

^dPatients without target lesions at baseline per independent review who achieved non-complete response/non-progressive disease.

syndrome was the most common treatment-emergent adverse event that led to discontinuation of sunitinib (n = 4 [0.9%]). Among Japanese patients, treatment-emergent adverse events led to discontinuation of avelumab in 6 patients (18.2%), axitinib in 1 patient (3.0%), and both avelumab and axitinib in 0 patients, and led to discontinuation of sunitinib in 4 patients (11.8%). Treatment-emergent adverse events that led to discontinuation of avelumab were infusion-related reaction (n = 2 [6.1%]), diarrhea, vomiting, hepatic function abnormal, liver disorder and interstitial lung disease (n = 1 each [3.0%]); those that led to discontinuation of axitinib were anal hemorrhage, hemorrhoids and proctalgia (n = 1 each [3.0%]). Treatment-emergent adverse events that led to discontinuation of sunitinib were cerebellar hemorrhage, drug eruption (erythema), oculomucocutaneous syndrome and proteinuria (n = 1 each [2.9%]). Treatment-related adverse events are detailed in Table S3. In the overall population, deaths due to study treatment toxicity occurred in 3 patients (0.7%; due to sudden death, myocarditis and necrotizing pancreatitis) and 1 patient (0.2%; due to intestinal perforation) in the avelumab + axitinib and sunitinib arms, respectively²³; however, no treatment-related deaths were observed among Japanese patients in either treatment arm.

Of the 33 Japanese patients who received avelumab + axitinib, 20 (60.6%) experienced adverse events categorized as immune-related

adverse events according to a prespecified case definition; 4 (12.1%) experienced grade ≥3 events. The most frequent immune-related adverse events were immune-related thyroid disorders, which were observed in 17 patients (51.5%) who received avelumab + axitinib. Grade 3 immune-related adverse events of hyperthyroidism, hepatic function abnormal and diarrhea (n = 1 each) and 1 grade 4 event of liver disorder were observed. No immune-related adverse events resulted in death. High-dose glucocorticoids (≥40 mg total daily dose of prednisone or equivalent) were administered to 3 Japanese patients (9.1%) who experienced an immune-related adverse event with avelumab + axitinib, whereas 48 patients (11.1%) received high-dose glucocorticoids in the overall population.²³

3.5 | Subsequent therapy

As in the overall population, a smaller proportion of Japanese patients in the combination arm than those in the sunitinib arm received subsequent anticancer drug therapies: 7 (21.2%) vs 12 (35.3%), respectively (Table S4).²³ At the time of data cutoff, most patients who had received subsequent anticancer therapy had received 1 follow-up therapeutic regimen (Table S4). Among Japanese patients, the most frequently used subsequent anticancer drug therapies (in >5% of patients) were sunitinib (9.1%),

TABLE 4 Antitumor activity per BICR in patients irrespective of PD-L1 expression

Characteristic	Overall population (N = 886)		Japanese patients (N = 67)	
	Avelumab + axitinib (N = 442)	Sunitinib (N = 444)	Avelumab + axitinib (N = 33)	Sunitinib (N = 34)
Confirmed objective response rate (95% CI), %	51.4 (46.6, 56.1)	25.7 (21.7, 30.0)	60.6 (42.1, 77.1)	17.6 (6.8, 34.5)
Stratified odds ratio (95% CI) ^a	3.10 (2.300, 4.148)		6.89 (2.047, 25.715)	
Confirmed best overall response, n (%)				
Complete response	15 (3.4)	8 (1.8)	0	1 (2.9)
Partial response	212 (48.0)	106 (23.9)	20 (60.6)	5 (14.7)
Stable disease	131 (29.6)	202 (45.5)	10 (30.3)	18 (52.9)
Progressive disease	51 (11.5)	83 (18.7)	2 (6.1)	7 (20.6)
Not evaluable	25 (5.7) ^b	35 (7.9) ^c	0	1 (2.9) ^d
Other ^e	8 (1.8)	10 (2.3)	1 (3.0)	2 (5.9)
Median time to response (range), months	2.6 (1.2, 13.8)	3.2 (1.2, 11.6)	2.8 (1.3, 5.6)	2.8 (1.4, 7.0)
Patients with ongoing response, n/total n (%)	158/227 (69.6)	81/114 (71.1)	12/20 (60.0)	6/6 (100.0)

Note: Data for overall population are from reference 23. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; PD-L1, programmed death-ligand 1.

^aOdds ratio >1 indicates better outcome with avelumab + axitinib compared to sunitinib.

^bNo postbaseline assessments due to early death or other reasons such as withdrawal of consent (n = 18); stable disease <6 wk after randomization (n = 5); no adequate baseline assessment (n = 2).

^cStable disease <6 wk after randomization (n = 15); no postbaseline assessments due to early death or other reasons such as withdrawal of consent (n = 14); new anticancer therapy started before first postbaseline assessment (n = 3); no adequate baseline assessment (n = 2); all postbaseline assessments have overall response of not evaluable (n = 1).

^dStable disease <6 wk after randomization.

^ePatients without target lesions at baseline per independent review who achieved non-complete response/non-progressive disease.

everolimus (6.1%), and axitinib (6.1%) in the combination arm and nivolumab (29.4%) and axitinib (14.7%) in the sunitinib arm (Table S5).

4 | DISCUSSION

The phase 3 JAVELIN Renal 101 trial demonstrated significantly longer PFS and higher ORR for avelumab + axitinib than with sunitinib in previously untreated patients with advanced RCC.²³ To our knowledge, this is the first report of the safety and efficacy of a first-line regimen of immune checkpoint inhibitor + tyrosine kinase inhibitor in Japanese patients. Among Japanese patients enrolled in JAVELIN Renal 101, treatment with avelumab + axitinib also resulted in longer PFS and higher ORR than treatment with sunitinib. Similar results were observed by BICR and investigator assessment.

Median PFS in the overall population and Japanese patients with PD-L1+ tumors who received avelumab + axitinib was 13.8 months and not estimable, respectively; in patients who received sunitinib, median PFS was 7.2 and 11.2 months, respectively. ORRs were 55.2% and 68.2%, respectively, in the overall

population and Japanese patients with PD-L1+ tumors who received the combination and 25.5% and 15.0%, respectively, in patients who received sunitinib. Median PFS in the overall population and Japanese patients irrespective of PD-L1 expression who received avelumab + axitinib was 13.8 and 16.6 months, respectively; in patients who received sunitinib, median PFS was 8.4 and 11.2 months, respectively. ORRs were 51.4% and 60.6%, respectively, in the overall population and Japanese patients irrespective of PD-L1 expression who received the combination, and 25.7% and 17.6%, respectively, in patients who received sunitinib. The demographic and disease characteristics of the Japanese patients do not offer a clear explanation for the longer median PFS observed in both arms of the trial, because fewer Japanese patients with favorable IMDC/MSKCC risk, more with stage IV disease, and more with a shorter time from histopathological diagnosis to randomization were enrolled than patients in the overall population. However, potential reasons could be the modestly higher proportion of Japanese patients with ECOG PS of 0 than patients in the overall population (approximately 80% vs 60%) and the lower proportion of Japanese patients with ≥3 tumor sites than patients in the overall population (approximately 10% vs 20%).

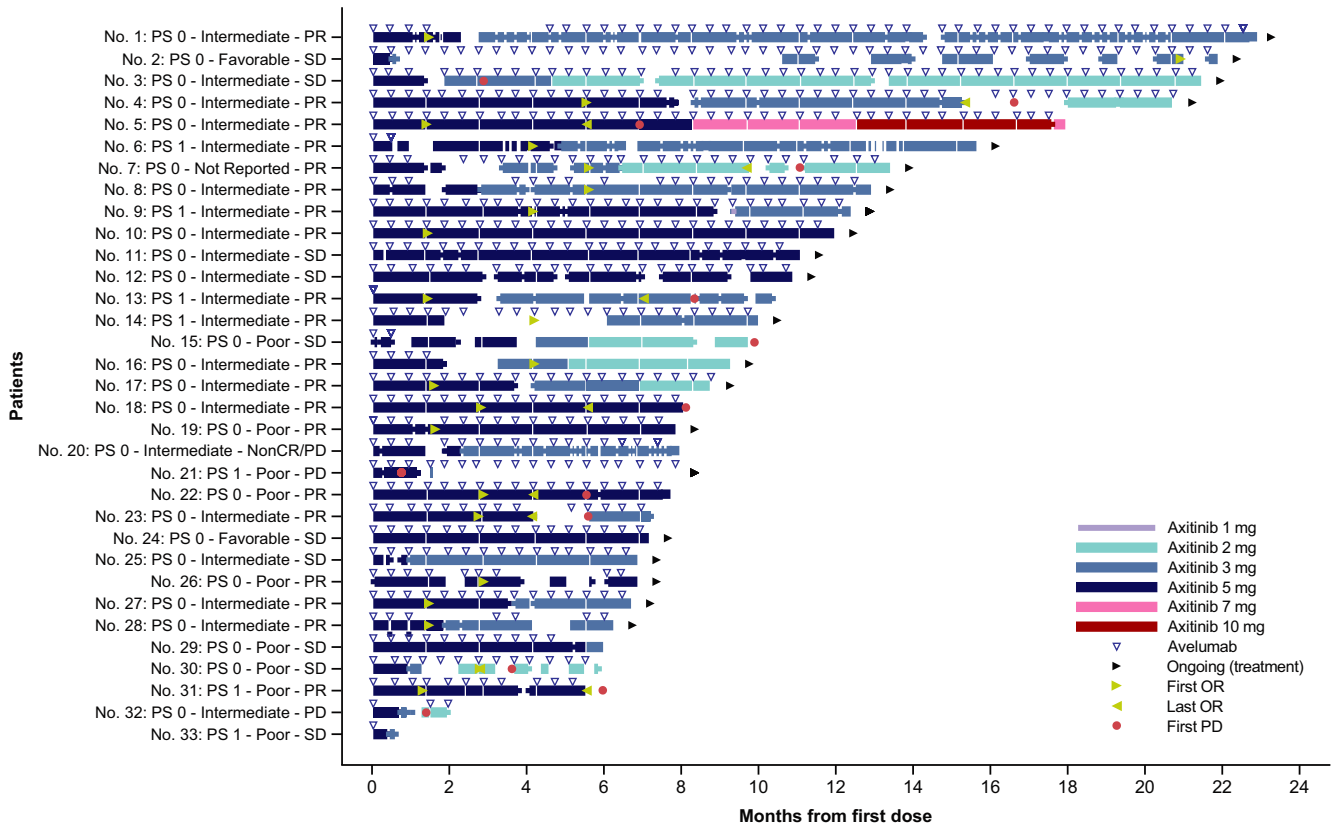


FIGURE 2 Duration of treatment and time to and duration of response with avelumab + axitinib per BICR in Japanese patients irrespective of PD-L1 expression (N = 33). Vertical axis label: ECOG PS from IRT system; IMDC risk category; and best overall response based on BICR assessment. The thin bar indicates axitinib treatment once daily. Patient 21 temporarily stopped axitinib, but the permanent discontinuation of axitinib had not been judged by the investigator at the data cutoff date. It is recorded in the clinical database that the treatment with axitinib was still ongoing for this patient. BICR, blinded independent central review; CR, complete response; OR, objective response; PD, progressive disease; PD-L1, programmed death- ligand 1; PR, partial response; PS, performance status; SD, stable disease

The Japanese patients with either PD-L1+ tumors or irrespective of PD-L1 expression who were treated with avelumab + axitinib rapidly showed tumor response after the start of treatment (median time to response: 1.6 or 2.8 months, respectively) and the response continued in the majority of Japanese patients (73.3% or 60.0% as of the data cutoff date, which was similar to that in the overall population. Analysis following long-term follow-up is warranted to evaluate the durable response with avelumab + axitinib.

The median duration of treatment was similar between the overall population and Japanese patients; however, more Japanese patients had at least one dose reduction of axitinib or sunitinib, resulting in lower median relative dosing intensity with both study drugs, but these dose reductions did not affect efficacy in Japanese patients. Importantly, the response was maintained after axitinib dose reduction in the majority of Japanese patients treated with avelumab + axitinib.

In Japanese patients who received avelumab + axitinib, common any-grade adverse events were hand-foot syndrome, hypertension, hypothyroidism, diarrhea and dysphonia, which are frequently reported toxicities associated with VEGF/VEGFR inhibition,^{4,27-29} with hypertension being the most

common grade ≥ 3 adverse event (30.3%). The safety profile in Japanese patients enrolled in this trial was similar to that in the overall population, with the exceptions of hand-foot syndrome and hypothyroidism, which occurred more frequently in Japanese patients than in the overall population (63.6% vs 33.4% and 54.5% vs 24.9%, respectively). Higher rates of adverse events have been reported in Japanese or Asian patients with RCC who received VEGF/VEGFR inhibitors than in non-Asian patients,^{13-15,18,19,30-34} which is potentially attributed to differences in ethnicity or genetic background. The rate of discontinuation of avelumab due to adverse events in Japanese patients was comparable to that in the overall population (18.2% vs 19.4%), whereas the rate of discontinuation of axitinib due to adverse events in Japanese patients was lower than that in the overall population (3.0% vs 12.9%). The rate of discontinuation of both avelumab and axitinib due to adverse events in Japanese patients was also lower than that in the overall population (0% vs 7.6%). Despite the higher incidence of adverse events in Japanese patients, adverse events were well managed with axitinib dose reduction and/or interruption.

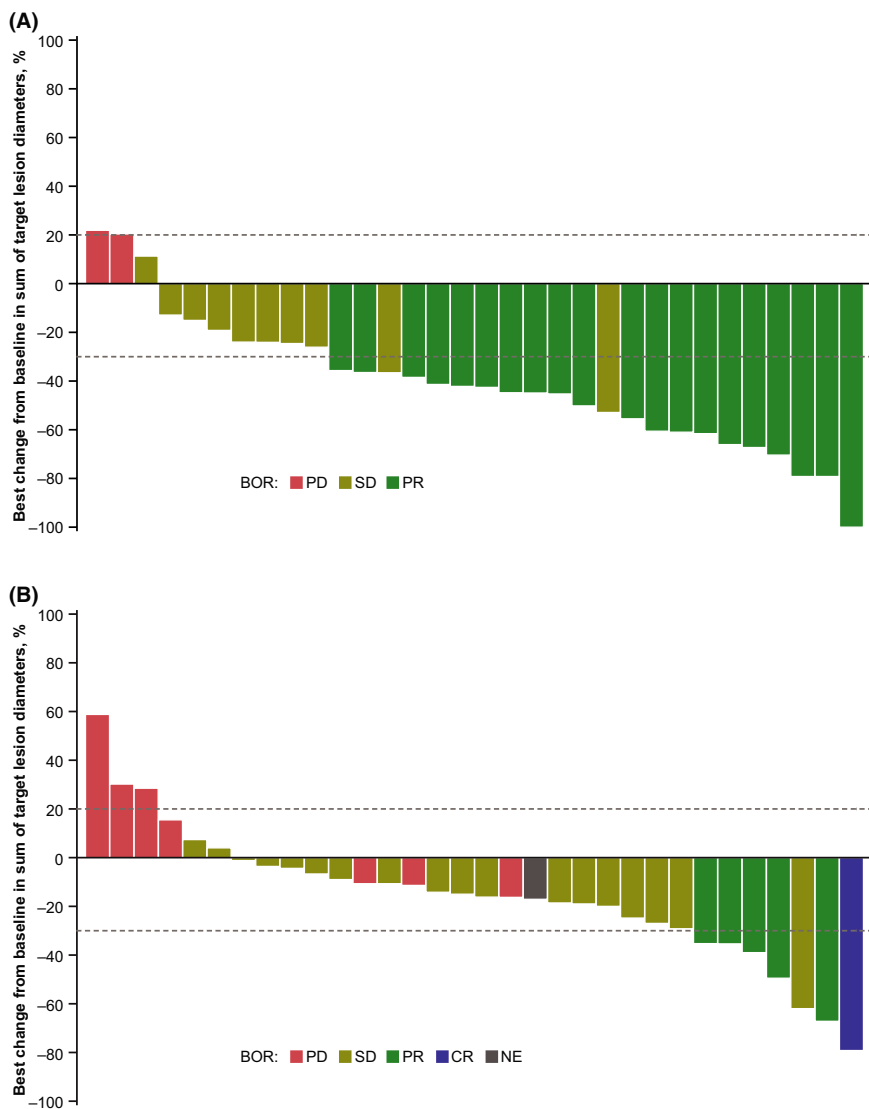


FIGURE 3 Best percentage change from baseline in target lesions per BICR in Japanese patients irrespective of PD-L1 expression who received avelumab + axitinib (A) or sunitinib (B). BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease

The frequency of immune-related adverse events in Japanese patients treated with avelumab + axitinib was also higher than that in the overall population (60.6% vs 38.2%).²³ The most frequent immune-related adverse events were thyroid disorders in both Japanese patients and the overall population. Thyroid disorders showed the largest difference in frequency between Japanese patients and the overall population (51.5% vs 24.7%), which caused the higher frequency of total immune-related adverse events observed in Japanese patients. However, it was previously reported that the incidence of hypothyroidism with axitinib treatment alone was also higher in Japanese patients than the overall population in the studies of single-agent axitinib in patients with advanced RCC.^{14,19} The trend of higher frequency of hypothyroidism in Japanese patients compared to the overall population was observed with other VEGFR inhibitors, such as sorafenib and regorafenib.^{14,35} In addition, immune-related thyroid disorders observed in Japanese patients did not require corticosteroid therapy. The incidence of other immune-related adverse events such as hepatitis, colitis, adrenal

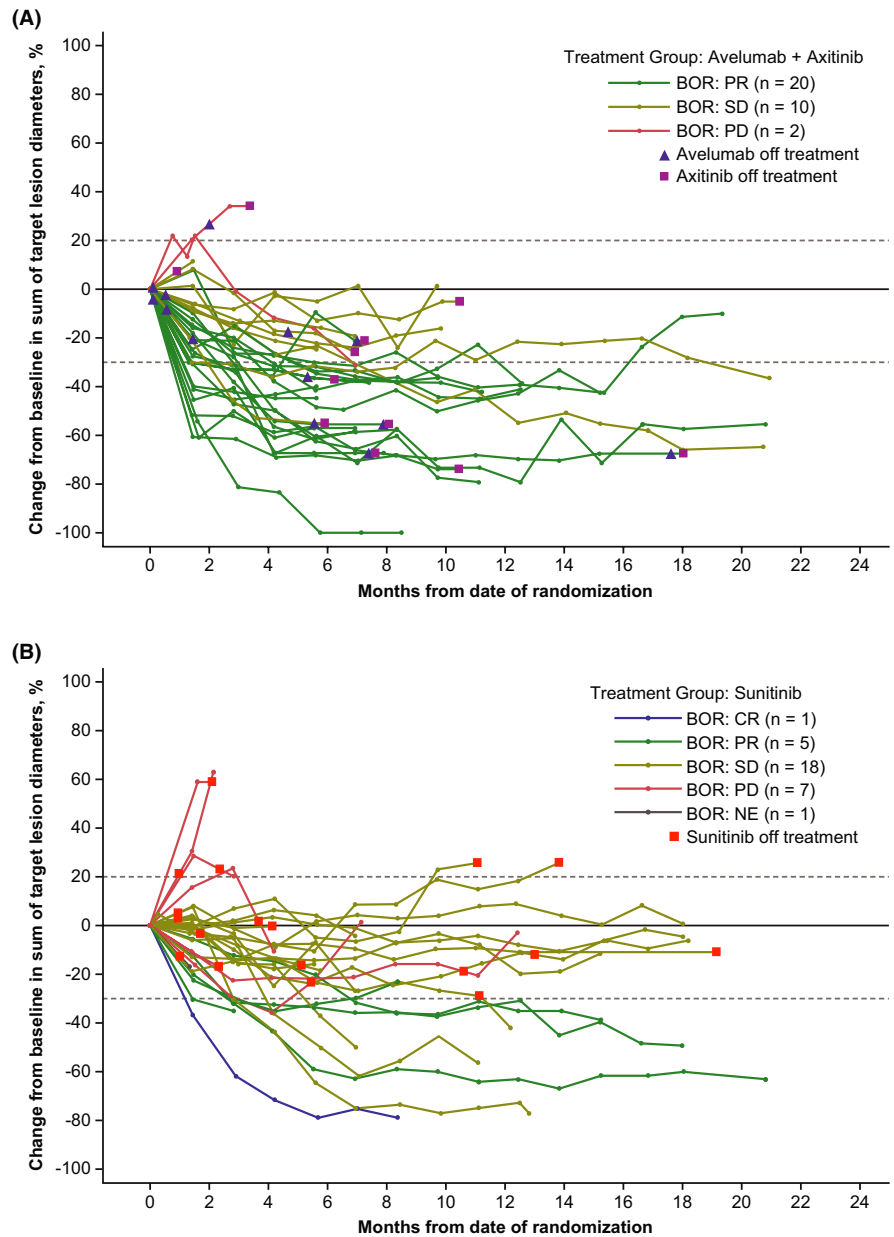
insufficiency or rash was similar between Japanese patients and the overall population. Furthermore, the incidence of patients who required high-dose glucocorticoids was similar between Japanese patients and the overall population (9.1% vs 11.1%). Taken together, the overall safety profile for immune-related adverse events was similar between Japanese patients and the overall population.

In conclusion, the combination of avelumab + axitinib was efficacious and tolerable in Japanese patients with treatment-naive advanced RCC, which is consistent with the results in the overall trial population. Thus, avelumab + axitinib is considered to be a first-line treatment option for Japanese patients with advanced RCC.

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FIGURE 4 Percent change from baseline in target lesions per BICR in Japanese patients irrespective of PD-L1 expression who received avelumab + axitinib (A) or sunitinib (B). BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease



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DISCLOSURE

Motohide Uemura has nothing to disclose. Yoshihiko Tomita has received honoraria from Pfizer, Astellas, Novartis, Ono, Sanofi-Aventis and BMS; reports a consulting or advisory role for Novartis, Ono, Taiho and MSD; and reports institutional research funding from Pfizer, Ono, Takeda and Astellas. Hideaki Miyake has nothing to disclose. Shingo Hatakeyama has received honoraria from Pfizer, Astellas, Kissei, Sanofi and Ono; and reports institutional research funding from Pfizer, Astellas, Kissei, Sanofi, Ono, Bristol, Janssen and Kaneka. Hiro-omi Kanayama has received honoraria from Pfizer and reports institutional research funding from Pfizer. Kazuyuki Numakura has received honoraria from Pfizer, Astellas, Ono, Kyowa Kirin and AstraZeneca, and research funding from the Ministry of Education (Japan; Grants-in-Aid for Scientific Research).

TABLE 5 Exposure to study drugs among all treated patients

	Overall population (N = 873)			Japanese patients (N = 67)		
	Avelumab (N = 434)	Axitinib (N = 434)	Sunitinib (N = 439)	Avelumab (N = 33)	Axitinib (N = 33)	Sunitinib (N = 34)
Duration of treatment, median (range), months ^a	8.6 (0.5, 25.3)	9.0 (0.02, 24.9)	7.3 (0.2, 23.0)	7.8 (0.5, 23.0)	8.7 (0.6, 22.8)	8.4 (0.5, 23.0)
Total number of infusions received, median (range)	18 (1, 55)	NA	NA	16 (1, 48)	NA	NA
Patients with at least one infusion rate reduction of 50% or more, n (%)	67 (15.4)	NA	NA	5 (15.2)	NA	NA
Patients with at least one infusion interruption, n (%)	43 (9.9)	NA	NA	0	NA	NA
Patients with dose reduction, n (%) ^b	21 (4.8)	183 (42.2)	187 (42.6)	2 (6.1)	23 (69.7)	25 (73.5)
Patients with dose escalation, n (%)	NA	47 (10.8)	NA	NA	1 (3.0)	NA
Relative dose intensity, median (range), %	91.5 (23.3, 107.3)	89.4 (6.1, 193.4)	83.9 (21.4, 148.2)	89.8 (23.3, 103.3)	69.4 (18.3, 138.5)	55.5 (24.6, 100.0)

Note: Data for overall population are from reference 23.

Abbreviation: NA, not applicable.

^aAvelumab: Time period starting from date of the first dose to date of the last dose + 14 or data cutoff. Axitinib: Time period starting from date of the first dose to date of the last dose + 1 or data cutoff. Sunitinib: Time period starting from date of the first dose to date of the last dose + d or data cutoff, where d is 1 if the patient discontinues sunitinib prior to the end of the last cycle or 14 otherwise.

^bAvelumab: Dose reduction is defined as actual non-zero dose <90% of the planned dose.

TABLE 6 Adverse events of any grade that occurred in ≥15% of patients in either arm or adverse events of grade ≥3 that occurred in ≥5% of patients in either arm among all treated patients

Preferred term n (%)	Overall population (N = 873)				Japanese patients (N = 67)			
	Avelumab + axitinib (N = 434)		Sunitinib (N = 439)		Avelumab + axitinib (N = 33)		Sunitinib (N = 34)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with any events	432 (99.5)	309 (71.2)	436 (99.3)	314 (71.5)	33 (100.0)	21 (63.6)	34 (100.0)	29 (85.3)
Diarrhea	270 (62.2)	29 (6.7)	209 (47.6)	12 (2.7)	16 (48.5)	3 (9.1)	16 (47.1)	1 (2.9)
Hypertension	215 (49.5)	111 (25.6)	158 (36.0)	75 (17.1)	18 (54.5)	10 (30.3)	15 (44.1)	6 (17.6)
Fatigue	180 (41.5)	15 (3.5)	176 (40.1)	16 (3.6)	0	0	2 (5.9)	0
Nausea	148 (34.1)	6 (1.4)	172 (39.2)	7 (1.6)	7 (21.2)	0	8 (23.5)	0
Hand-foot syndrome	145 (33.4)	25 (5.8)	148 (33.7)	19 (4.3)	21 (63.6)	3 (9.1)	24 (70.6)	3 (8.8)
Dysphonia	133 (30.6)	2 (0.5)	14 (3.2)	0	15 (45.5)	0	2 (5.9)	0
Decreased appetite	114 (26.3)	9 (2.1)	126 (28.7)	4 (0.9)	10 (30.3)	2 (6.1)	8 (23.5)	0
Hypothyroidism	108 (24.9)	1 (0.2)	61 (13.9)	1 (0.2)	18 (54.5)	0	8 (23.5)	0
Stomatitis	102 (23.5)	8 (1.8)	103 (23.5)	4 (0.9)	13 (39.4)	1 (3.0)	12 (35.3)	0
Cough	100 (23.0)	1 (0.2)	83 (18.9)	0	4 (12.1)	0	5 (14.7)	0
Headache	89 (20.5)	1 (0.2)	71 (16.2)	1 (0.2)	3 (9.1)	0	3 (8.8)	0
Dyspnea	86 (19.8)	13 (3.0)	57 (13.0)	7 (1.6)	1 (3.0)	0	0	0
Arthralgia	85 (19.6)	4 (0.9)	50 (11.4)	2 (0.5)	3 (9.1)	0	2 (5.9)	0
Weight decreased	85 (19.6)	12 (2.8)	30 (6.8)	4 (0.9)	3 (9.1)	1 (3.0)	0	0
Vomiting	80 (18.4)	4 (0.9)	87 (19.8)	7 (1.6)	5 (15.2)	0	1 (2.9)	0
Back pain	77 (17.7)	2 (0.5)	65 (14.8)	8 (1.8)	4 (12.1)	0	1 (2.9)	0
Constipation	77 (17.7)	0	64 (14.6)	0	8 (24.2)	0	6 (17.6)	0
ALT increased	74 (17.1)	26 (6.0)	50 (11.4)	11 (2.5)	6 (18.2)	4 (12.1)	3 (8.8)	1 (2.9)
Chills	69 (15.9)	1 (0.2)	33 (7.5)	0	1 (3.0)	0	0	0

(Continues)

TABLE 6 (Continued)

Preferred term n (%)	Overall population (N = 873)				Japanese patients (N = 67)			
	Avelumab + axitinib (N = 434)		Sunitinib (N = 439)		Avelumab + axitinib (N = 33)		Sunitinib (N = 34)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Asthenia	64 (14.7)	11 (2.5)	72 (16.4)	13 (3.0)	0	0	0	0
AST increased	63 (14.5)	17 (3.9)	52 (11.8)	9 (2.1)	4 (12.1)	2 (6.1)	6 (17.6)	2 (5.9)
Dysgeusia	57 (13.1)	0	142 (32.3)	0	7 (21.2)	0	19 (55.9)	0
Pyrexia	56 (12.9)	0	62 (14.1)	1 (0.2)	8 (24.2)	0	16 (47.1)	1 (2.9)
Infusion-related reaction	53 (12.2)	7 (1.6)	0	0	9 (27.3)	1 (3.0)	0	0
Epistaxis	37 (8.5)	0	49 (11.2)	0	4 (12.1)	0	9 (26.5)	0
Dyspepsia	35 (8.1)	0	83 (18.9)	0	2 (6.1)	0	4 (11.8)	0
Nasopharyngitis	31 (7.1)	0	27 (6.2)	0	8 (24.2)	0	4 (11.8)	0
Lipase increased	28 (6.5)	18 (4.1)	27 (6.2)	18 (4.1)	1 (3.0)	1 (3.0)	3 (8.8)	3 (8.8)
Anemia	26 (6.0)	7 (1.6)	101 (23.0)	36 (8.2)	2 (6.1)	2 (6.1)	10 (29.4)	6 (17.6)
Proteinuria	26 (6.0)	7 (1.6)	14 (3.2)	4 (0.9)	6 (18.2)	0	6 (17.6)	2 (5.9)
GGT increased	25 (5.8)	13 (3.0)	20 (4.6)	11 (2.5)	3 (9.1)	3 (9.1)	3 (8.8)	2 (5.9)
Hyperthyroidism	24 (5.5)	3 (0.7)	6 (1.4)	0	4 (12.1)	2 (6.1)	0	0
Amylase increased	23 (5.3)	6 (1.4)	13 (3.0)	4 (0.9)	5 (15.2)	1 (3.0)	3 (8.8)	3 (8.8)
Thrombocytopenia	15 (3.5)	1 (0.2)	85 (19.4)	27 (6.2)	0	0	2 (5.9)	2 (5.9)
Malaise	10 (2.3)	0	21 (4.8)	2 (0.5)	6 (18.2)	0	16 (47.1)	1 (2.9)
Platelet count decreased	8 (1.8)	0	63 (14.4)	22 (5.0)	1 (3.0)	0	22 (64.7)	11 (32.4)
Hepatic function abnormal	7 (1.6)	5 (1.2)	3 (0.7)	2 (0.5)	6 (18.2)	4 (12.1)	3 (8.8)	2 (5.9)
Neutropenia	6 (1.4)	1 (0.2)	83 (18.9)	35 (8.0)	0	0	1 (2.9)	1 (2.9)
WBC count decreased	2 (0.5)	0	37 (8.4)	10 (2.3)	1 (3.0)	0	11 (32.4)	6 (17.6)
Lymphocyte count decreased	1 (0.2)	0	20 (4.6)	5 (1.1)	0	0	6 (17.6)	2 (5.9)
Neutrophil count decreased	1 (0.2)	0	45 (10.3)	25 (5.7)	1 (3.0)	0	11 (32.4)	9 (26.5)

Note: Data for overall population are from reference 23. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase; WBC, white blood cell.

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DATA-SHARING STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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