

ORIGINAL RESEARCH

Efficacy and safety of avelumab plus axitinib in elderly patients with advanced renal cell carcinoma: extended follow-up results from JAVELIN Renal 101

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Background: In the phase III JAVELIN Renal 101 trial, first-line avelumab plus axitinib demonstrated a progression-free survival (PFS) and objective response rate (ORR) benefit versus sunitinib in patients with advanced renal cell carcinoma (aRCC). However, efficacy in elderly patients remains unclear. We report efficacy and safety by age group from the second interim analysis of overall survival (OS).

Patients and methods: PFS and ORR as per blinded independent central review (RECIST 1.1), OS, and safety were assessed in patient groups aged <65, ≥65 to <75, and ≥75 years.

Results: In the avelumab plus axitinib and sunitinib arms, 271/138/33 and 275/128/41 patients aged <65, ≥65 to <75, and ≥75 years, respectively, were randomized. At data cut-off (January 2019), median PFS [95% confidence interval (CI)] with avelumab plus axitinib versus sunitinib in these respective age groups was 11.6 (8.4-19.4) versus 6.9 (5.6-8.4) months [hazard ratio (HR), 0.63; 95% CI 0.501-0.786], 13.8 (11.1-18.0) versus 11.0 (7.8-16.6) months (HR, 0.88; 95% CI 0.627-1.231), and 13.8 [7.0-not estimable (NE)] versus 9.8 (4.3-NE) months (HR, 0.76; 95% CI 0.378-1.511). Median OS (95% CI) in the respective age groups was not reached (NR) (NE-NE) versus 28.6 (25.5-NE) months (HR, 0.74; 95% CI 0.541-1.022), 30.0 (30.0-NE) versus NR (NE-NE) months (HR, 0.89; 95% CI 0.546-1.467), and 25.3 (19.9-NE) versus NR (19.4-NE) months (HR, 0.87; 95% CI 0.359-2.106). ORR (95% CI) in the respective age groups was 49.4% (43.3% to 55.6%) versus 27.3% (22.1% to 32.9%), 60.9% (52.2% to 69.1%) versus 28.9% (21.2% to 37.6%), and 42.4% (25.5% to 60.8%) versus 22.0% (10.6% to 37.6%). In the avelumab plus axitinib arm, grade ≥3 adverse events (AEs) and immune-related AEs occurred in 76.9%/81.2%/72.7% and 45.5%/48.1%/36.4% in the respective age groups.

Conclusions: First-line avelumab plus axitinib demonstrated favorable efficacy across age groups, including patients aged ≥75 years. OS data were still immature; follow-up is ongoing. The safety profile was generally consistent across age groups.

Key words: immune checkpoint inhibitor, elderly, avelumab plus axitinib, phase III, renal cell carcinoma

INTRODUCTION

Many renal cell carcinomas (RCCs) express programmed death-ligand 1 (PD-L1) and harbor genetic mutations that increase the production of vascular endothelial growth

factor (VEGF).¹ The interaction between PD-L1 and programmed cell death protein 1 (PD-1) reduces immunosurveillance, while VEGF promotes angiogenesis. Consistent with this, RCCs are sensitive to immunotherapies, and patients with RCC benefit from antiangiogenic drugs that target VEGF or its receptors (VEGFRs).^{1,2} As a result, combinations of immune checkpoint inhibitors (ICIs) and VEGF/VEGFR inhibitors have garnered interest as treatments for advanced RCC (aRCC).^{1,3,4}

Avelumab is an anti-PD-L1 human immunoglobulin G1 monoclonal antibody that has been approved as a

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monotherapy for metastatic Merkel cell carcinoma and urothelial cancer.^{5,6} Axitinib is a highly selective VEGFR tyrosine kinase inhibitor that is approved as a second-line treatment for aRCC.⁷⁻¹² Axitinib has also shown antitumor activity and a manageable safety profile in patients with metastatic RCC in the first-line setting in randomized studies.¹³⁻¹⁶ At the first interim analysis of the phase III JAVELIN Renal 101 (NCT02684006) trial, avelumab combined with axitinib demonstrated significantly longer progression-free survival (PFS) and a higher objective response rate (ORR) than the prior standard of care, sunitinib, in both PD-L1-positive patients and the overall population.¹⁷ Based on these data, combination therapy with avelumab plus axitinib was approved as a first-line treatment for aRCC in the United States, Europe, and Japan.^{6,18,19}

The updated efficacy results at the second interim analysis of overall survival (OS) (minimum follow-up, 13 months) showed that avelumab plus axitinib conferred a PFS benefit and nearly doubled the ORR compared with sunitinib.²⁰ The median PFS in the overall population was 13.3 [95% confidence interval (CI) 11.1-15.3] months with avelumab plus axitinib compared with 8.0 (95% CI 6.7-9.8) months with sunitinib [hazard ratio (HR), 0.69; 95% CI 0.574-0.825; one-sided $P < 0.0001$].²⁰ The ORR in the overall population was 52.5% (95% CI 47.7% to 57.2%) with a complete response (CR) rate of 3.8% in the avelumab plus axitinib arm versus an ORR of 27.3% (95% CI 23.2% to 31.6%) and a CR rate of 2.0% in the sunitinib arm.²⁰

Although ICIs have revolutionized the treatment landscape for aRCC, their impact in elderly patients is not yet clear.^{21,22} Older age, particularly between 75 and 84 years, is a major risk factor for the development of solid cancers, including RCCs.²² Immunosenescence, the decline of immune activity in elderly patients, promotes cancer development due to an inability to combat carcinogenesis.^{21,22} Immunosenescence might impact how elderly patients respond to immunotherapy in a myriad of ways.²¹ Immunosenescence involves reduced T-cell activity, including proliferation and survival after T-cell receptor stimulation, and a lower number of naïve CD8-positive T cells.²¹ Furthermore, cytotoxic T cells, a critical antitumor effector cell in the PD-1/PD-L1 pathway, show reduced proliferative capacity and increased sensitivity to apoptotic signals in elderly patients.²¹ In addition, antigen-presenting cell-mediated responses are impeded in elderly patients due to a decrease in co-signaling molecules on the surface of dendritic cells (e.g. CD80 and CD40) and T cells (e.g. CD28).²¹ For these reasons, it was hypothesized that ICIs might be less effective in elderly patients than in younger patients.²¹

Unfortunately, studies investigating novel ICIs for the treatment of various cancers, including aRCC, lack comprehensive analyses of response and toxicity in patients older than 65 years.^{17,20,23} Nonetheless, a recent meta-analysis indicated that elderly patients (>65 years) with metastatic RCC likely benefit more from immunotherapy and VEGFR inhibitor combinations than from sunitinib.²³ Similarly, a retrospective analysis of genitourinary cancers,

RCC, and urothelial carcinoma suggested that ICI safety and efficacy was comparable between patients aged <75 and ≥75 years.²² The Expanded Access Program (EAP) in Italy showed comparable efficacy and safety of nivolumab between elderly patients (≥70 or ≥75 years) and the overall population with metastatic RCC.²⁴ Although these studies lack comprehensive analyses, they suggest that ICIs might be efficacious and safe in elderly populations.

Overall, information on the safety and efficacy of ICIs combined with VEGFR inhibitors in elderly patients is sparse. Although the combination of avelumab and axitinib showed favorable OS, PFS, and ORR compared with sunitinib regardless of age (<65 or ≥65 years), a thorough assessment of the safety and efficacy in elderly patients with aRCC is lacking.^{17,20} Here, we report a comprehensive analysis of the efficacy and safety of avelumab plus axitinib versus sunitinib by age group, including patients aged ≥75 years, from the second interim analysis of OS in the JAVELIN Renal 101 trial.

PATIENTS AND METHODS

Study design and participants

The trial was a phase III, multicenter, randomized, open-label study comparing avelumab plus axitinib with sunitinib. Full trial details were previously described.¹⁷ Briefly, eligible participants were adults with previously untreated aRCC with a clear-cell component, at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines, defined by the International Council for Harmonisation. All participating patients provided written informed consent.

Study treatment

The study treatment was detailed previously.¹⁷ Avelumab was administered at a dose of 10 mg/kg of body weight as a 1-h intravenous infusion every 2 weeks. Axitinib was taken 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 were carried out as described previously.¹⁷

Assessments

The two independent primary endpoints were PFS as per RECIST version 1.1 according to blinded independent central review (BICR) and OS in patients with PD-L1-positive tumors (≥1% of immune cells staining positive within the tumor area of the tissue sample). PD-L1 expression was assessed at a central laboratory with the Ventana PD-L1 (SP263) assay (Ventana Medical Systems, Tucson, AZ). Key secondary endpoints were PFS as determined by BICR according to RECIST version 1.1 and OS in patients in the overall

population, irrespective of PD-L1 expression. Other secondary endpoints were ORR, best overall response, and adverse events (AEs). Tumors were assessed using computed tomography or magnetic resonance imaging as previously described.¹⁷ AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.03.¹⁷ We conducted subgroup analyses of these endpoints in patients <65, ≥65 to <75, and ≥75 years of age.

Statistical analysis

Statistical analyses were carried out as previously described.^{17,20} The second preplanned interim analysis of OS was based on a data cut-off time point when ~336 PFS events by BICR occurred in patients with PD-L1-positive tumors, and the last randomized patient had been followed up for ≥12 months after randomization (preplanned final analysis of PFS and second interim analysis of OS). All data reported here are based on the second interim analysis.

Efficacy endpoints were assessed in all patients who underwent randomization, and safety was evaluated in all patients who received at least one dose of a trial drug (avelumab, axitinib, or sunitinib).

Post hoc analyses for efficacy and safety by age group (<65, ≥65 to <75, and ≥75 years) were conducted. PFS and OS were estimated using the Kaplan–Meier method; unstratified HRs and corresponding 95% CIs are reported. The ORR and corresponding 95% CI were calculated for each age group using the Clopper–Pearson method. PFS and best overall response were assessed by BICR (RECIST version 1.1).

RESULTS

Patients

Between 29 March 2016 and 19 December 2017, a total of 886 patients with aRCC were randomized to the avelumab plus axitinib arm ($n = 442$) or the sunitinib arm ($n = 444$).¹⁷ Of patients assigned to the avelumab plus axitinib arm, 271, 138, and 33 were aged <65, ≥65 to <75, and ≥75 years, respectively. In the sunitinib arm, 275, 128, and 41 patients were aged <65, ≥65 to <75, and ≥75 years, respectively. Baseline demographics and disease characteristics were balanced between the two arms in each age group (Table 1). The proportion of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups was generally well balanced between both treatment arms, with slightly more patients aged ≥75 years with intermediate risk in the avelumab plus axitinib arm than in the sunitinib arm and slightly more patients aged ≥75 years with favorable risk in the sunitinib arm than in the avelumab plus axitinib arm. Similarly, in patients aged ≥75 years, the prevalence of ECOG PS 0 was higher in the avelumab plus axitinib arm than in the sunitinib arm, and the prevalence of ECOG PS 1 was higher in the sunitinib arm than in the avelumab plus axitinib arm. The median times from histopathological diagnosis to randomization were different

in patients aged <65, ≥65 to <75, and ≥75 years in both arms (5.2, 11.5, and 11.4 months in the avelumab plus axitinib arm versus 4.9, 6.1, and 20.9 months in the sunitinib arm). Numbers and locations of tumor sites outside the kidney and PD-L1 statuses were similar in both treatment arms across age groups. The proportion of tumor sites located in the kidney was slightly higher in patients aged ≥75 years compared with other age groups in both treatment arms.

Efficacy

At the data cut-off for the second interim analysis of OS (28 January 2019), the median duration of follow-up for PFS and OS was 16.8 (95% CI 16.5–17.9) and 19.3 (95% CI 18.6–20.0) months, respectively, in the avelumab plus axitinib arm and 15.2 (95% CI 14.0–16.6) and 19.2 (95% CI 18.3–19.8) months, respectively, in the sunitinib arm. The median PFS in the intention-to-treat (ITT) population was 13.3 (95% CI 11.1–15.3) months with avelumab plus axitinib versus 8.0 (95% CI 6.7–9.8) months with sunitinib (stratified HR, 0.69; 95% CI 0.574–0.825) (Figure 1A).²⁰ In patients aged <65 years, the median PFS was 11.6 (95% CI 8.4–19.4) months with avelumab plus axitinib versus 6.9 (95% CI 5.6–8.4) months with sunitinib (unstratified HR, 0.63; 95% CI 0.501–0.786). In patients aged ≥65 to <75 years, the median PFS was 13.8 (95% CI 11.1–18.0) months with avelumab plus axitinib versus 11.0 (95% CI 7.8–16.6) months with sunitinib (unstratified HR, 0.88; 95% CI 0.627–1.231). In patients aged ≥75 years, the median PFS was 13.8 [95% CI 7.0–not estimable (NE)] months with avelumab plus axitinib versus 9.8 (4.3–NE) months with sunitinib (unstratified HR, 0.76; 95% CI 0.378–1.511) (Figure 1B–D).

The median OS in the ITT population was not reached (NR) (95% CI 30.0 months–NE) with avelumab plus axitinib versus NR (95% CI 27.4 months–NE) with sunitinib (stratified HR, 0.80; 95% CI 0.616–1.027) (Figure 1E).²⁰ The median OS in patients aged <65 years was NR (95% CI NE–NE) with avelumab plus axitinib versus 28.6 (95% CI 25.5–NE) months with sunitinib (unstratified HR, 0.74; 95% CI 0.541–1.022). The median OS in patients aged ≥65 to <75 years was 30.0 (95% CI 30.0–NE) months with avelumab plus axitinib versus NR (95% CI NE–NE) with sunitinib (unstratified HR, 0.89; 95% CI 0.546–1.467). The median OS in patients aged ≥75 years was 25.3 (95% CI 19.9–NE) months with avelumab plus axitinib versus NR (95% CI 19.4 months–NE) with sunitinib (unstratified HR, 0.87; 95% CI 0.359–2.106) (Figure 1F–H).

In the ITT population, the ORR was 52.5% with avelumab plus axitinib compared with 27.3% with sunitinib (Figure 1I and J).²⁰ Furthermore, the CR rate was 3.8% in the avelumab plus axitinib group versus 2.0% in the sunitinib group.²⁰ In patients who received avelumab plus axitinib, the ORR was 49.4% (95% CI 43.3% to 55.6%), 60.9% (95% CI 52.2% to 69.1%), and 42.4% (95% CI 25.5% to 60.8%) in patients aged <65, ≥65 to <75, and ≥75 years, respectively, with CR rates of 4.4%, 2.2%, and 6.1%, respectively (Figure 1I and Supplementary Table S1, available at <https://doi.org/10.1016/j.esmoop.2022.100450>). In the sunitinib

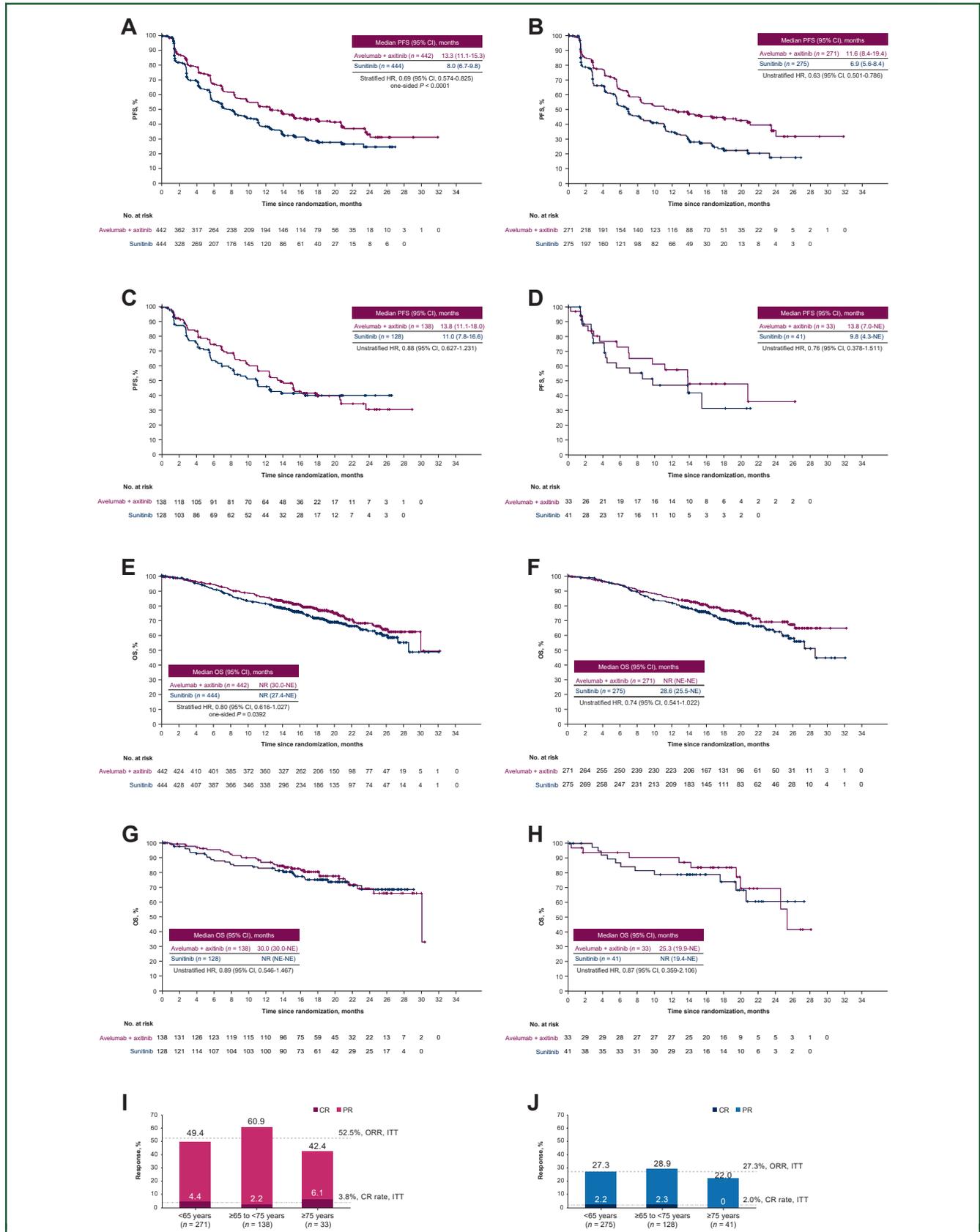


Figure 1. PFS (as per BICR assessment), OS, and ORR and CR (as per BICR assessment) in the ITT population and by age group in the avelumab + axitinib and sunitinib arms.

(A) PFS in the ITT population, (B) PFS in patients aged <65 years, (C) PFS in patients aged ≥65 to <75 years, (D) PFS in patients aged ≥75 years, (E) OS in the ITT population, (F) OS in patients aged <65 years, (G) OS in patients aged ≥65 to <75 years, (H) OS in patients aged ≥75 years, (I) ORR and CR by age group in the avelumab + axitinib arm, and (J) ORR and CR by age group in the sunitinib arm.

BICR, blinded independent central review; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; NE, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response. Figure 1A and E are reused from Choueiri et al.²⁰

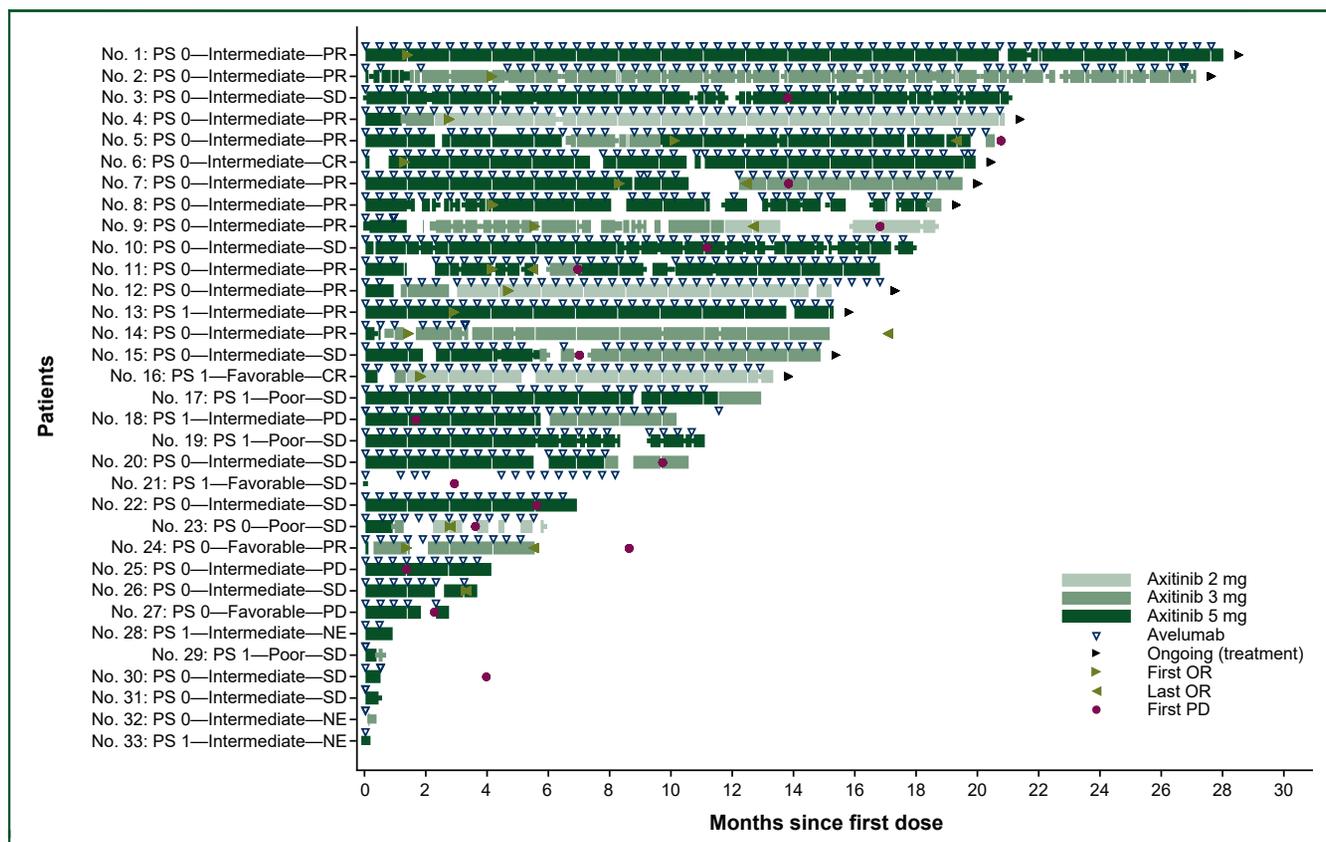


Figure 2. Treatment duration and time to and duration of response as per BICR in the avelumab + axitinib arm, age ≥ 75 years. Data are patient number: ECOG PS from Interactive Response Technology system—IMDC risk category—best overall response on BICR assessment (RECIST v1.1). The thin bar indicates QD. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NE, not evaluable; OR, objective response; PD, progressive disease; PR, partial response; SD, stable disease; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

group, the ORR in patients aged < 65 , ≥ 65 to < 75 , and ≥ 75 years, respectively, was 27.3% (95% CI 22.1% to 32.9%), 28.9% (95% CI 21.2% to 37.6%), and 22.0% (95% CI 10.6% to 37.6%), respectively, with CR rates of 2.2%, 2.3%, and 0%, respectively (Figure 1J and Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2022.100450>).

The best percentage change and percentage change from baseline in the sum of target-lesion diameters as per BICR is shown for each age group in both treatment arms (Supplementary Figures S1 and S2, available at <https://doi.org/10.1016/j.esmooop.2022.100450>). The treatment duration for each patient aged ≥ 75 years in the avelumab plus axitinib arm is shown, along with ECOG PS, IMDC risk group, best overall response, time to response, and duration of response as per BICR (Figure 2). Of the 33 patients aged ≥ 75 years, 2 had a CR and 12 had a partial response.

Of the two patients who had a CR, one was a 75-year-old white woman initially diagnosed with stage IV cancer with intermediate IMDC risk (one risk factor, hemoglobin level less than the lower limit of normal), ECOG PS of 0, nephrectomy, and Fuhrman grade 3 at 3.6 months from histopathological diagnosis to randomization. The target tumor size was 40.6 mm (lung 24.4 mm, lung 16.2 mm), and nontarget tumors were found in the kidney and lung. The other patient who had a CR was a 78-year-old black or

African American woman initially diagnosed with stage I cancer with favorable IMDC risk, ECOG PS of 1, nephrectomy, and Fuhrman grade 3 at 95.4 months from histopathological diagnosis to randomization. The target tumor size was 24.2 mm (liver 13.6 mm, liver 10.6 mm), and nontarget tumors were found in the lung.

Exposure

Exposure to study drugs by age group is shown in Table 2. The median duration (range) of treatment in patients aged < 65 , ≥ 65 to < 75 , and ≥ 75 years, respectively, was 14.0 (0.5-32.2), 13.3 (0.5-29.9), and 11.1 (0.5-28.1) months with avelumab; 14.3 (0.1-32.2), 13.3 (0.1-29.9), and 12.9 (0.03-28.0) months with axitinib; and 7.6 (0.4-27.7), 10.9 (0.4-27.3), and 8.4 (0.2-26.2) months with sunitinib. The median (range) relative dose intensity in patients aged < 65 , ≥ 65 to < 75 , and ≥ 75 years, respectively, was 92.4% (28.0% to 106.9%), 91.4% (23.3% to 106.9%), and 88.2% (27.8% to 101.8%) with avelumab; 91.4% (6.1% to 195.4%), 82.0% (20.9% to 152.6%), and 84.7% (34.4% to 100.0%) with axitinib; and 87.5% (35.0% to 104.4%), 76.4% (35.7% to 103.6%), and 68.3% (21.4% to 148.2%) with sunitinib.

In patients who received axitinib in the combination group, 107 (39.9%) patients aged < 65 years, 72 (54.1%) patients aged ≥ 65 to < 75 years, and 18 (54.5%) patients

Table 1. Baseline demographics and clinical characteristics of patients by age group

Characteristic	Avelumab + axitinib			Sunitinib		
	<65 years n = 271	≥65 to <75 years n = 138	≥75 years n = 33	<65 years n = 275	≥65 to <75 years n = 128	≥75 years n = 41
Age, median (range), years	56.0 (29.0-64.0)	68.0 (65.0-74.0)	79.0 (75.0-83.0)	56.0 (27.0-64.0)	68.0 (65.0-74.0)	77.0 (75.0-88.0)
Sex, n (%)						
Male	198 (73.1)	93 (67.4)	25 (75.8)	219 (79.6)	95 (74.2)	30 (73.2)
Female	73 (26.9)	45 (32.6)	8 (24.2)	56 (20.4)	33 (25.8)	11 (26.8)
Weight, median (range), kg	81.0 (46.0-143.3)	83.0 (44.2-134.4)	74.5 (49.3-105.3)	86.2 (48.0-193.1)	80.0 (41.4-148.2)	72.3 (46.7-111.2)
Race, n (%)						
Black or African American	7 (2.6)	2 (1.4)	1 (3.0)	6 (2.2)	3 (2.3)	1 (2.4)
American Indian or Alaska native	3 (1.1)	1 (0.7)	0	4 (1.5)	0	0
Asian	47 (17.3)	16 (11.6)	7 (21.2)	39 (14.2)	19 (14.8)	5 (12.2)
Native Hawaiian or other Pacific Islander	0	0	0	0	1 (0.8)	0
White	198 (73.1)	111 (80.4)	23 (69.7)	209 (76.0)	94 (73.4)	31 (75.6)
Other	4 (1.5)	5 (3.6)	0	8 (2.9)	5 (3.9)	1 (2.4)
Unknown	12 (4.4)	3 (2.2)	2 (6.1)	9 (3.3)	6 (4.7)	3 (7.3)
ECOG PS, n (%)						
0	180 (66.4)	81 (58.7)	23 (69.7)	177 (64.4)	82 (64.1)	17 (41.5)
1	91 (33.6)	56 (40.6)	10 (30.3)	97 (35.3)	46 (35.9)	24 (58.5)
2	0	0	0	1 (0.4)	0	0
Not reported	0	1 (0.7)	0	0	0	0
IMDC prognostic risk, n (%)						
Favorable	52 (19.2)	38 (27.5)	4 (12.1)	56 (20.4)	30 (23.4)	10 (24.4)
Intermediate	166 (61.3)	80 (58.0)	25 (75.8)	174 (63.3)	77 (60.2)	25 (61.0)
Poor	50 (18.5)	18 (13.0)	4 (12.1)	44 (16.0)	21 (16.4)	6 (14.6)
Not reported	3 (1.1)	2 (1.4)	0	1 (0.4)	0	0
Previous nephrectomy, n (%)						
Yes	217 (80.1)	110 (79.7)	25 (75.8)	226 (82.2)	98 (76.6)	31 (75.6)
No	54 (19.9)	28 (20.3)	8 (24.2)	49 (17.8)	30 (23.4)	10 (24.4)
Time from histopathological diagnosis to randomization, median (range), months	5.2 (0.4-240.8)	11.5 (0.7-428.9)	11.4 (0.8-267.9)	4.9 (0.2-225.6)	6.1 (0.5-354.0)	20.9 (0.4-268.1)
Time from recurrence/metastatic disease to randomization, median (range), months	1.9 (0.2-119.9)	3.2 (0.1-193.0)	2.2 (0.2-243.9)	2.1 (0.2-64.1)	2.3 (0.0-75.0)	2.9 (0.4-53.7)
RECIST-defined number of target tumor sites at baseline as per BICR, n (%)						
0	8 (3.0)	2 (1.4)	0	9 (3.3)	5 (3.9)	0
1	111 (41.0)	56 (40.6)	11 (33.3)	105 (38.2)	55 (43.0)	18 (43.9)
2	86 (31.7)	53 (38.4)	11 (33.3)	96 (34.9)	42 (32.8)	14 (34.1)
3	45 (16.6)	17 (12.3)	7 (21.2)	51 (18.5)	19 (14.8)	6 (14.6)
≥4	21 (7.7)	10 (7.2)	4 (12.1)	14 (5.1)	7 (5.5)	3 (7.3)
Tumor sites at baseline as per BICR in lung only, n (%)						
Yes	27 (10.0)	19 (13.8)	4 (12.1)	26 (9.5)	15 (11.7)	3 (7.3)
No	244 (90.0)	119 (86.2)	29 (87.9)	249 (90.5)	113 (88.3)	38 (92.7)
Tumor sites at baseline as per BICR, n (%)						
Lung	198 (73.1)	108 (78.3)	26 (78.8)	194 (70.5)	89 (69.5)	25 (61.0)
Lymph node	126 (46.5)	59 (42.8)	11 (33.3)	140 (50.9)	59 (46.1)	16 (39.0)
Bone	57 (21.0)	36 (26.1)	4 (12.1)	65 (23.6)	31 (24.2)	13 (31.7)
Liver	54 (19.9)	25 (18.1)	4 (12.1)	42 (15.3)	18 (14.1)	6 (14.6)
Kidney	51 (18.8)	24 (17.4)	12 (36.4)	48 (17.5)	27 (21.1)	14 (34.1)
Pancreas	16 (5.9)	12 (8.7)	5 (15.2)	5 (1.8)	6 (4.7)	5 (12.2)
Brain	10 (3.7)	2 (1.4)	0	8 (2.9)	6 (4.7)	1 (2.4)
PD-L1 status						
Positive	165 (60.9)	86 (62.3)	19 (57.6)	189 (68.7)	79 (61.7)	22 (53.7)
Negative	80 (29.5)	42 (30.4)	10 (30.3)	70 (25.5)	39 (30.5)	11 (26.8)
Unknown	26 (9.6)	10 (7.2)	4 (12.1)	16 (5.8)	10 (7.8)	8 (19.5)

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

aged ≥75 years had at least one dose reduction. In the sunitinib arm, 101 (37.0%) patients aged <65 years, 73 (57.9%) patients aged ≥65 to <75 years, and 22 (55.0%) patients aged ≥75 years had at least one dose reduction. In patients who received axitinib, 38 (14.2%) and 9 (6.8%)

patients aged <65 and ≥65 to <75 years, respectively, received a dose escalation. No patients aged ≥75 years received a dose escalation. In patients who received avelumab, the total number of infusions is also shown (Table 2), along with infusion rate reduction and interruption.

Table 2. Exposure to study drugs among all treated patients by age group

	Avelumab			Axitinib			Sunitinib		
	<65 years n = 268	≥65 to <75 years n = 133	≥75 years n = 33	<65 years n = 268	≥65 to <75 years n = 133	≥75 years n = 33	<65 years n = 273	≥65 to <75 years n = 126	≥75 years n = 40
Duration of treatment, median (range), months ^a	14.0 (0.5-32.2)	13.3 (0.5-29.9)	11.1 (0.5-28.1)	14.3 (0.1-32.2)	13.3 (0.1-29.9)	12.9 (0.03-28.0)	7.6 (0.4-27.7)	10.9 (0.4-27.3)	8.4 (0.2-26.2)
Total number of infusions received, median (range)	26.5 (1-70)	26 (1-60)	22 (1-61)	NA	NA	NA	NA	NA	NA
Patients with at least one infusion rate reduction of 50% or more, n (%)	45 (16.8)	20 (15.0)	3 (9.1)	NA	NA	NA	NA	NA	NA
Patients with at least one infusion interruption, n (%)	32 (11.9)	11 (8.3)	2 (6.1)	NA	NA	NA	NA	NA	NA
Patients with dose reduction, n (%) ^b	15 (5.6)	3 (2.3)	3 (9.1)	107 (39.9)	72 (54.1)	18 (54.5)	101 (37.0)	73 (57.9)	22 (55.0)
Patients with dose escalation, n (%)	NA	NA	NA	38 (14.2)	9 (6.8)	0	NA	NA	NA
Relative dose intensity, median (range), %	92.4 (28.0-106.9)	91.4 (23.3-106.9)	88.2 (27.8-101.8)	91.4 (6.1-195.4)	82.0 (20.9-152.6)	84.7 (34.4-100.0)	87.5 (35.0-104.4)	76.4 (35.7-103.6)	68.3 (21.4-148.2)

NA, not applicable.
^a Avelumab: time period starting from the date of the first dose to the date of the last dose + 14 or data cut-off; axitinib: time period starting from the date of the first dose to the date of the last dose + 1 or data cut-off; sunitinib: time period starting from the date of the first dose to the date of the last dose + d or data cut-off, where d is 1 if the patient discontinues sunitinib before the end of the last cycle or 14 otherwise.
^b Avelumab: dose reduction is defined as actual nonzero dose <90% of the planned dose.

Safety

The safety profile was generally consistent across age groups in both arms (Table 3). In the avelumab plus axitinib arm, AEs of any grade during treatment occurred in 268 (100%), 133 (100%), and 33 (100%) patients aged <65, ≥65 to <75, and ≥75 years, respectively, and grade ≥3 AEs occurred in 206 (76.9%), 108 (81.2%), and 24 (72.7%) patients aged <65, ≥65 to <75, and ≥75 years, respectively. Similarly, in the sunitinib arm, 271 (99.3%), 125 (99.2%), and 40 (100%) patients aged <65, ≥65 to <75, and ≥75 years, respectively, experienced AEs, and grade ≥3 AEs occurred in 196 (71.8%), 109 (86.5%), and 31 (77.5%) patients aged <65, ≥65 to <75, and ≥75 years, respectively. The most common AEs in all age groups in both treatment arms were diarrhea, hypertension, fatigue, hand-foot syndrome, and nausea. In the avelumab plus axitinib arm, infusion-related reaction was reported in 36 (13.4%), 17 (12.8%), and 3 (9.1%) patients aged <65, ≥65 to <75, and ≥75 years, respectively.

AEs leading to avelumab discontinuation occurred in 20.1%, 25.6%, and 36.4% of patients aged <65, ≥65 to <75, and ≥75 years, respectively. AEs leading to axitinib discontinuation occurred in 14.9%, 17.3%, and 33.3% of patients aged <65, ≥65 to <75, and ≥75 years, respectively. AEs leading to sunitinib discontinuation occurred in 12.1%, 19.0%, and 17.5% of patients aged <65, ≥65 to <75, and ≥75 years, respectively (Supplementary Table S2, available at <https://doi.org/10.1016/j.esmooop.2022.100450>).

Of patients who received avelumab plus axitinib, 122 (45.5%), 64 (48.1%), and 12 (36.4%) aged <65, ≥65 to <75, and ≥75 years, respectively, experienced immune-related AEs (irAEs), and 31 (11.6%), 19 (14.3%), and 5 (15.2%) aged <65, ≥65 to <75, and ≥75 years, respectively, experienced grade ≥3 irAEs (Table 3). The most frequent irAEs were immune-related thyroid disorders, which occurred in 83 (31.0%), 38 (28.6%), and 6 (18.2%) patients aged <65, ≥65 to <75, and ≥75 years, respectively. Of patients who received avelumab plus axitinib, 31 (11.6%), 24 (18.0%), and 5 (15.2%) aged <65, ≥65 to <75, and ≥75 years, respectively, were treated with high-dose corticosteroids (≥40 mg total daily dose of prednisone or equivalent).

DISCUSSION

Although the combination of ICI and VEGFR inhibitors for the treatment of aRCC has gained traction, the safety and efficacy of this treatment in elderly patients has not been characterized.^{1,21,22} Given that elderly patients undergo immunosenescence, it has been hypothesized that immunotherapies might not offer elderly patients the same benefits observed in younger patients.^{21,22} Here, we investigated the efficacy and safety of avelumab plus axitinib by age group in patients with aRCC from the JAVELIN Renal 101 trial.¹⁷

The baseline demographics and clinical characteristics were generally well balanced across all age groups in both treatment groups. The proportion of patients with ECOG PS 0 was higher in the avelumab plus axitinib arm than in the sunitinib arm in patients aged ≥75 years, whereas the

Table 3. Treatment-emergent adverse events (≥20% frequency^a) and irAEs by age group

Treatment-emergent adverse events												
n (%)	Avelumab + axitinib						Sunitinib					
	<65 years n = 268		≥65 to <75 years n = 133		≥75 years n = 33		<65 years n = 273		≥65 to <75 years n = 126		≥75 years n = 40	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event	268 (100)	206 (76.9)	133 (100)	108 (81.2)	33 (100)	24 (72.7)	271 (99.3)	196 (71.8)	125 (99.2)	109 (86.5)	40 (100)	31 (77.5)
Diarrhea	180 (67.2)	23 (8.6)	95 (71.4)	12 (9.0)	17 (51.5)	3 (9.1)	142 (52.0)	7 (2.6)	61 (48.4)	5 (4.0)	17 (42.5)	1 (2.5)
Hypertension	138 (51.5)	72 (26.9)	68 (51.1)	39 (29.3)	19 (57.6)	10 (30.3)	99 (36.3)	41 (15.0)	45 (35.7)	30 (23.8)	17 (42.5)	11 (27.5)
Fatigue	108 (40.3)	7 (2.6)	73 (54.9)	9 (6.8)	10 (30.3)	1 (3.0)	110 (40.3)	8 (2.9)	59 (46.8)	7 (5.6)	18 (45.0)	2 (5.0)
Hand-foot syndrome	107 (39.9)	19 (7.1)	43 (32.3)	9 (6.8)	5 (15.2)	0	95 (34.8)	12 (4.4)	51 (40.5)	5 (4.0)	12 (30.0)	2 (5.0)
Nausea	97 (36.2)	5 (1.9)	55 (41.4)	3 (2.3)	8 (24.2)	0	105 (38.5)	5 (1.8)	59 (46.8)	2 (1.6)	17 (42.5)	0
Dysphonia	85 (31.7)	1 (0.4)	48 (36.1)	0	10 (30.3)	1 (3.0)	10 (3.7)	0	5 (4.0)	0	2 (5.0)	0
Hypothyroidism	83 (31.0)	3 (1.1)	39 (29.3)	0	5 (15.2)	0	45 (16.5)	1 (0.4)	21 (16.7)	0	6 (15.0)	1 (2.5)
Cough	78 (29.1)	0	41 (30.8)	1 (0.8)	6 (18.2)	0	65 (23.8)	0	23 (18.3)	0	7 (17.5)	0
Decreased appetite	72 (26.9)	7 (2.6)	44 (33.1)	3 (2.3)	9 (27.3)	0	69 (25.3)	3 (1.1)	54 (42.9)	1 (0.8)	15 (37.5)	1 (2.5)
Stomatitis	72 (26.9)	3 (1.1)	36 (27.1)	5 (3.8)	3 (9.1)	0	67 (24.5)	1 (0.4)	35 (27.8)	1 (0.8)	7 (17.5)	2 (5.0)
Headache	68 (25.4)	0	28 (21.1)	1 (0.8)	4 (12.1)	0	51 (18.7)	0	22 (17.5)	2 (1.6)	6 (15.0)	0
Dyspnea	62 (23.1)	9 (3.4)	28 (21.1)	1 (0.8)	4 (12.1)	2 (6.1)	38 (13.9)	5 (1.8)	20 (15.9)	1 (0.8)	6 (15.0)	0
Back pain	59 (22.0)	2 (0.7)	28 (21.1)	2 (1.5)	3 (9.1)	0	45 (16.5)	4 (1.5)	26 (20.6)	4 (3.2)	8 (20.0)	0
Arthralgia	57 (21.3)	3 (1.1)	32 (24.1)	1 (0.8)	7 (21.2)	0	38 (13.9)	2 (0.7)	14 (11.1)	1 (0.8)	6 (15.0)	0
Constipation	55 (20.5)	0	30 (22.6)	0	5 (15.2)	0	37 (13.6)	0	27 (21.4)	0	8 (20.0)	0
Pruritus	55 (20.5)	0	24 (18.0)	0	5 (15.2)	0	15 (5.5)	0	7 (5.6)	0	4 (10.0)	0
Abdominal pain	54 (20.1)	4 (1.5)	18 (13.5)	1 (0.8)	2 (6.1)	0	39 (14.3)	9 (3.3)	13 (10.3)	1 (0.8)	5 (12.5)	0
Weight decreased	52 (19.4)	7 (2.6)	33 (24.8)	6 (4.5)	8 (24.2)	1 (3.0)	18 (6.6)	3 (1.1)	15 (11.9)	2 (1.6)	5 (12.5)	0
Vomiting	52 (19.4)	3 (1.1)	33 (24.8)	3 (2.3)	3 (9.1)	0	55 (20.1)	5 (1.8)	29 (23.0)	1 (0.8)	13 (32.5)	1 (2.5)
ALT increased	50 (18.7)	17 (6.3)	29 (21.8)	11 (8.3)	4 (12.1)	1 (3.0)	28 (10.3)	8 (2.9)	14 (11.1)	1 (0.8)	4 (10.0)	2 (5.0)

irAEs with avelumab + axitinib						
n (%)	<65 years n = 268		≥65 to <75 years n = 133		≥75 years n = 33	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any irAE	122 (45.5)	31 (11.6)	64 (48.1)	19 (14.3)	12 (36.4)	5 (15.2)
Thyroid disorder	83 (31.0)	4 (1.5)	38 (28.6)	1 (0.8)	6 (18.2)	0
Rash	20 (7.5)	4 (1.5)	15 (11.3)	1 (0.8)	3 (9.1)	0
Hepatitis	16 (6.0)	12 (4.5)	13 (9.8)	7 (5.3)	2 (6.1)	2 (6.1)
Colitis	13 (4.9)	7 (2.6)	5 (3.8)	3 (2.3)	1 (3.0)	1 (3.0)
Adrenal insufficiency	8 (3.0)	2 (0.7)	5 (3.8)	0	1 (3.0)	1 (3.0)
Type I diabetes mellitus	4 (1.5)	2 (0.7)	3 (2.3)	1 (0.8)	0	0
Pneumonitis	3 (1.1)	0	0	0	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0	1 (3.0)	1 (3.0)
Pituitary dysfunction	1 (0.4)	0	0	0	0	0
Renal dysfunction	0	0	3 (2.3)	3 (2.3)	0	0
Pancreatitis	0	0	3 (2.3)	3 (2.3)	0	0
Patients receiving high-dose ^b corticosteroids for an irAE	31 (11.6)		24 (18.0)		5 (15.2)	

ALT, alanine aminotransferase; irAE, immune-related adverse event.

^a 20% cut-off defined on frequency of AEs in either age group in the avelumab + axitinib arm only.

^b High-dose is defined as ≥40 mg of the total daily dose of prednisone or the equivalent.

percentage of patients in the favorable IMDC risk group was higher in the sunitinib arm than in the avelumab plus axitinib arm in patients aged ≥ 75 years. The proportion of patients with PD-L1-positive tumors was comparable among age groups in both treatment arms.

Avelumab plus axitinib demonstrated favorable efficacy in both PFS and OS compared with sunitinib across age groups, including patients aged ≥ 75 years. The HRs for both PFS and OS were higher in patients aged ≥ 65 to < 75 years and ≥ 75 years than in patients aged < 65 years. Interestingly, median PFS and median OS were shorter in patients aged < 65 years than in patients aged ≥ 65 to < 75 years and ≥ 75 years in the sunitinib arm. This might potentially explain the lower HR in patients aged < 65 years compared with the other two groups. The reason why median PFS and median OS were shortest in the youngest age group in the sunitinib arm is unclear. The demographics and clinical characteristics were generally similar among age groups in the sunitinib arm. The magnitude of HRs for both PFS and OS was comparable in patients aged ≥ 65 to < 75 years and ≥ 75 years. It is likely that patients aged ≥ 75 years will obtain a benefit that is similar to that in patients aged ≥ 65 to < 75 years. The ORR in avelumab plus axitinib was higher than in sunitinib across age groups. A CR was observed in two patients aged ≥ 75 years receiving avelumab plus axitinib, whereas no patients aged ≥ 75 years experienced a CR in the sunitinib arm. Only 1 of 213 patients with metastatic RCC had a CR in a randomized phase II study of single-agent axitinib in the first-line setting.¹⁴

The duration of treatment was longer with avelumab and axitinib as compared with sunitinib regardless of age. The relative dose intensity was mostly similar across all age groups in both treatment arms. However, in the sunitinib arm, the relative dose intensity was lower in patients aged ≥ 75 years than in other age groups in the same arm. This trend was observed with sunitinib or pazopanib in a retrospective analysis based on age in patients with metastatic RCC; patients aged ≥ 75 years received a lower dose of sunitinib or pazopanib.²⁵

The safety profile was generally consistent among age groups in both the avelumab plus axitinib and sunitinib arms. The incidence of all-grade AEs and AEs grade ≥ 3 was comparable regardless of age group. The frequency of AEs leading to discontinuation of avelumab or axitinib was higher in patients aged ≥ 75 years than in other age groups. However, each AE for either avelumab or axitinib had only one patient discontinue treatment. Thus, no specific AE had a higher incidence of discontinuation. The incidence of patients who experienced an irAE or received high-dose corticosteroids for irAEs was comparable regardless of age group.

The safety and efficacy benefit observed in patients aged ≥ 75 years in the JAVELIN Renal 101 trial is consistent with prior reports of ICI-treated elderly patients with advanced cancer. A retrospective analysis demonstrated that patients aged ≥ 75 years with aRCC and urothelial carcinoma showed tumor response with ICIs.²² Furthermore, the incidence of irAEs was not significantly different in patients aged ≥ 75

versus < 75 years.²² Similarly, the Italian EAP study suggested that elderly patients (≥ 70 or ≥ 75 years) with metastatic RCC benefit from therapy with nivolumab, and the safety profile in elderly patients was consistent with that in the overall population.²⁴ A retrospective analysis showed that older patients (≥ 70 years) with metastatic RCC treated with ICIs had no difference in OS, time to treatment failure, or time to next treatment compared with younger patients.²⁶ Our efficacy findings are in agreement with these reports, and the incidence of irAEs was also similar across age groups, including patients aged ≥ 75 years. In a meta-analysis of patients aged ≥ 75 years with advanced cancer, including non-small-cell lung cancer, RCC, gastric cancer, and head and neck squamous cell carcinoma, ICIs appeared to be an effective treatment.²⁷ However, the survival benefit was observed with first-line treatment, and the efficacy in the second-line setting remains to be seen.²⁷ Thus, further investigations are needed to establish the safety and efficacy of ICIs as later treatments for elderly patients with advanced cancer.

Our study has some limitations. The sample size of patients aged ≥ 75 years in the JAVELIN Renal 101 trial is small (33 in the avelumab plus axitinib arm and 41 in the sunitinib arm). At our analysis based on the second interim analysis, the OS data were still immature; follow-up for the final analysis is ongoing.

Conclusions

Results from this subgroup analysis of the JAVELIN Renal 101 trial suggest that avelumab plus axitinib has favorable efficacy and consistent tolerability across age groups of patients with aRCC, including patients aged ≥ 75 years. OS data were still immature; follow-up is ongoing.

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DISCLOSURE

YT has received honoraria from Pfizer, Astellas Pharma, Novartis, Ono Pharmaceutical, Bristol Myers Squibb, and Chugai Pharma; has served in a consulting or advisory role

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affiliate of Merck KGaA, ESMO, Exelixis, Foundation Medicine, GlaxoSmithKline, Harborside Press, HERON, Ipsen, Kidney Cancer Association, *Lancet Oncology*, Lilly, Lpath, MSD, Michael J. Hennessy Associates, Navinata Health, NCCN, Novartis, Peloton Therapeutics, Pfizer, PlatformQ Health, Prometheus, Roche/Genentech, Sanofi/Aventis, *New England Journal of Medicine*, and UpToDate. BIR owns stock and other ownership interests in PTC Therapeutics; has served in a consulting or advisory role for Bristol Myers Squibb, Pfizer, Genentech/Roche, Aveo, Synthorx, Compugen, MSD, Corvus, Surface Oncology, 3D Medicines, Aravive, Alkermes, Arrowhead, GSK, and Shionogi; has received research funding paid to his institution, from Pfizer, MSD, Genentech/Roche, Aveo, AstraZeneca, Bristol Myers Squibb, and Exelixis; and has received travel, accommodations, and expenses from MSD, Pfizer, and Bristol Myers Squibb. HM has received honoraria; served in a consulting or advisory role for; and has received research funding paid to his institution from Pfizer. HU has received speakers' bureau fees from Pfizer, Bayer, MSD, Bristol Myers Squibb, and Janssen; and has received research funding paid to his institution from Takeda, Daiichi Sankyo, Astellas Pharma, Ono Pharmaceutical, AstraZeneca, Sanofi, and Kissei Pharmaceutical. LA has served in a consulting or advisory role for Amgen, Bristol Myers Squibb, Ipsen, Roche, Novartis, Pfizer, Astellas Pharma, Merck, MSD, AstraZeneca, Exelixis, Corvus, Peloton Therapeutics, Exelixis, and Janssen; has received research funding paid to her institution, from Bristol Myers Squibb; and has received travel, accommodations, and expenses from Bristol Myers Squibb and MSD. YF is an employee of Pfizer R&D Japan. YU is an employee of Pfizer R&D Japan and owns stock in Pfizer. JW is an employee of Pfizer and owns stock in Pfizer. MM is an employee of Pfizer. MS has received honoraria from Pfizer, Merck, Bristol Myers Squibb, MSD, Ipsen, Exelixis, Eisai, EUSA, and Alkermes; has served in a consulting or advisory role for Pfizer, Merck, Bristol Myers Squibb, MSD, Ipsen, Exelixis, Eisai, EUSA, and Alkermes; and has received travel, accommodations, and expenses from Pfizer, Roche, and Ipsen.

DATA SHARING

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

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