ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

# Association of C-reactive protein with efficacy of avelumab plus axitinib in advanced renal cell carcinoma: long-term follow-up results from JAVELIN Renal 101

**Y. Tomita[1*], J. Larkin[2], B. Venugopal[3], J. Haanen[4], H. Kanayama[5], M. Eto[6], M.-O. Grimm[7], Y. Fujii[8], Y. Umeyama[8], B. Huang[9], M. Mariani[10], A. di Pietro[10] & T. K. Choueiri[11]**

[1]Department of Urology, Department of Molecular Oncology, Niigata University Graduate School of Medicine, Niigata, Japan; [2]Department of Medical Oncology, Royal Marsden NHS Foundation Trust, London; [3]Institute of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [4]Division of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands; [5]Department of Urology, Tokushima University Graduate School of Biomedical Sciences, Tokushima; [6]Department of Urology, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan; [7]Department of Urology, Jena University Hospital, Jena, Germany; [8]Pfizer R&D Japan, Tokyo, Japan; [9]Pfizer, Groton, USA; [10]Pfizer SRL, Milan, Italy; [11]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, USA

Available online 28 August 2022

**Background:** C-reactive protein (CRP) is an important prognostic and predictive factor in advanced renal cell carcinoma (aRCC). We report the association of CRP levels at baseline and early after treatment with efficacy of avelumab plus axitinib or sunitinib from the phase III JAVELIN Renal 101 trial.

**Patients and methods:** Patients were categorized into normal (baseline CRP $<$10 mg/l), normalized (baseline CRP $\geq$10 mg/l and $\geq$1 CRP value decreased to $<$10 mg/l during 6-week treatment), and non-normalized (CRP $\geq$10 mg/l at baseline and during 6-week treatment) CRP groups. Progression-free survival and best overall response from the second interim analysis and overall survival (OS) from the third interim analysis were assessed.

**Results:** In the avelumab plus axitinib and sunitinib arms, respectively, 234, 51, and 108 patients and 232, 36, and 128 patients were categorized into normal, normalized, and non-normalized CRP groups. In respective CRP groups, objective response rates [95% confidence interval (CI)] were 56.0% (49.4% to 62.4%), 66.7% (52.1% to 79.2%), and 45.4% (35.8% to 55.2%) with avelumab plus axitinib and 30.6% (24.7% to 37.0%), 41.7% (25.5% to 59.2%), and 19.5% (13.1% to 27.5%) with sunitinib; complete response rates were 3.8%, 11.8%, and 0.9% and 3.0%, 0%, and 1.6%, respectively. Median progression-free survival (95% CI) was 15.2 months (12.5-21.0 months), not reached (NR) [11.1 months-not estimable (NE)], and 7.0 months (5.6-9.9 months) with avelumab plus axitinib and 11.2 months (8.4-13.9 months), 11.2 months (6.7-13.8 months), and 4.2 months (2.8-5.6 months) with sunitinib; median OS (95% CI) was NR (42.2 months-NE), NR (30.4 months-NE), and 23.0 months (18.4-33.1 months) and NR (39.0 months-NE), 39.8 months (21.7-NE), and 19.1 months (16.3-25.3 months), respectively. Multivariate analyses demonstrated that normalized or non-normalized CRP levels were independent factors for the prediction of objective response rate or OS, respectively, with avelumab plus axitinib.

**Conclusions:** In patients with aRCC, CRP levels at baseline and early after treatment may predict efficacy with avelumab plus axitinib.

**Key words:** renal cell carcinoma, immune checkpoint inhibitor, avelumab plus axitinib, predictive marker, phase III clinical trial, C-reactive protein

## INTRODUCTION

The most common type of renal cell carcinoma (RCC) is clear-cell RCC, which is associated with mutations that increase the production of vascular endothelial growth factor (VEGF).[1] Several antiangiogenic drugs that target VEGF and its receptors (VEGFRs) have shown significant treatment benefit in patients with advanced RCC (aRCC).[2] In addition to VEGF, many RCCs express programmed death-ligand 1 (PD-L1) on the tumor cell membrane and in tumor-infiltrating mononuclear cells.[1] Immune checkpoint inhibitors (ICIs) that target the interaction between PD-L1 and programmed death protein 1 (PD-1) have shown promising antitumor activity in patients with RCC.[3] As a

*Correspondence to: Yoshihiko Tomita, Department of Urology, Department of Molecular Oncology, Niigata University Graduate School of Medicine, Niigata 951-8510, Japan. Tel: +81-25-227-2289

E-mail: ytomita@med.niigata-u.ac.jp (Y. Tomita).

result, the combination of VEGF inhibitors and ICIs has been an area of considerable interest for treatment in patients with aRCC.[1,4]

Avelumab, a human immunoglobulin G1 monoclonal antibody that binds to PD-L1, has shown clinical activity and an acceptable safety profile as a single-agent treatment in aRCC.[5,6] Axitinib is a VEGFR tyrosine kinase inhibitor (TKI) approved for monotherapy in second-line treatment of aRCC.[2,7-11] Axitinib has also shown clinical activity and a manageable safety profile in the treatment of patients with metastatic RCC in the first-line setting.[12-15]

At the first interim analysis (IA1) of the phase III JAVELIN Renal 101 (NCT02684006) trial, treatment with avelumab in combination with axitinib resulted in significantly longer progression-free survival (PFS) and improved objective response rate (ORR) compared with sunitinib, the prior standard of care, in patients with PD-L1-positive tumors and in the overall population.[16] Based on these results, avelumab plus axitinib was approved as first-line treatment of aRCC in various countries.[17-19] At the second interim analysis (IA2), carried out after a minimum follow-up of 13 months, avelumab plus axitinib continued to show a significant improvement in PFS and nearly doubled the ORR compared with sunitinib.[20]

Serum C-reactive protein (CRP), one of the most intensively studied inflammatory factors, is an important prognostic and predictive factor in patients with aRCC. Elevated baseline CRP levels or changes in CRP levels after treatment have been associated with poor prognosis and efficacy outcomes in patients treated with various therapies, including cytokines[21,22] and TKIs.[23-30] In a randomized phase III study in patients with metastatic melanoma, patients with a low baseline CRP ($\leq 1.5 \times$ upper limit of normal) had a significant survival benefit with tremelimumab, an anti-cytotoxic T-lymphocyte antigen 4 monoclonal antibody, compared with chemotherapy. This was the first analysis that assessed the predictive effect of CRP with ICIs.[31] A more recent study showed that changes in CRP levels during early nivolumab (anti-PD-1) therapy were associated with efficacy, suggesting that a change in CRP levels may be a promising predictive biomarker for ICI monotherapy in patients with metastatic RCC.[32,33] The association between baseline CRP levels or changes in CRP levels and efficacy in patients treated with an ICI plus a VEGFR inhibitor, however, remains unclear. Here, we report the association of CRP levels at baseline and early in treatment with efficacy of avelumab plus axitinib or sunitinib in patients with aRCC from the long-term follow-up of the JAVELIN Renal 101 trial.

## MATERIAL AND METHODS

### Study design and participants

JAVELIN Renal 101 was a phase III, multicenter, randomized, open-label study comparing avelumab plus axitinib with sunitinib in patients with aRCC. Trial details were previously described.[16] Key eligibility criteria included adult patients with previously untreated aRCC with a clear-cell component, $\geq 1$ measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 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 patients provided written informed consent.

### Study treatment

Study treatments were previously described.[16] 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 modifications were carried out as previously described.

### Assessments

The two independent primary endpoints are PFS per RECIST 1.1 per blinded independent central review (BICR) and overall survival (OS) in patients with PD-L1-positive tumors ($\geq 1\%$ of immune cells staining positive within the tumor area of the tested tissue sample). Key secondary endpoints are PFS and OS in the overall patient population.

CRP levels were assessed at screening and on day 1 of each 6-week treatment cycle. CRP levels within 6 weeks (+3 days) after initiation of treatment were used for post-treatment analysis. Patients were categorized into three groups based on CRP levels at baseline and during treatment: normal, normalized, and non-normalized. Patients with baseline CRP $<10$ mg/l were placed in the normal CRP group. Patients with baseline CRP $\geq 10$ mg/l and $\geq 1$ CRP value that decreased to $<10$ mg/l during the 6 weeks after initiation of treatment were placed in the normalized CRP group. Patients with CRP $\geq 10$ mg/l at baseline and during the 6 weeks after initiation of treatment were placed in the non-normalized CRP group. The analysis population included all patients with CRP values available at both baseline and after treatment, in addition to patients who had a baseline CRP value available if the value was in the normal range (these patients were placed in the normal group) regardless of the availability of a post-treatment value. Efficacy in the normal CRP group was also explored in patients whose CRP on treatment was non-elevated (CRP $<10$ mg/l at baseline and during 6-week treatment) or elevated (CRP $<10$ mg/l at baseline and $\geq 1$ CRP value that increased to $\geq 10$ mg/l during 6-week treatment). The cut-off value for the CRP level was set at 10 mg/l, which is considered high based on a standard CRP test and was used as a cut-off in previously published studies.[32,34,35]

### Statistical analysis

Statistical analyses were carried out as previously described.[16,20] IA2 was based on a data cut-off time point when $\sim 336$ PFS events by BICR occurred in patients with PD-L1-positive tumors and the last randomized patient was followed for $\geq 12$ months after randomization. IA2 was the preplanned final analysis for PFS and the second interim

analysis for OS. As OS data were still immature at IA2, the third interim analysis (IA3) was conducted to assess OS, which was based on a data cut-off point 15 months after the pre-planned final analysis for PFS. In the current analysis, PFS and best overall response per RECIST 1.1 according to BICR were reported from IA2. OS was assessed from IA3. In the normalized CRP group, time from normalized to de-normalized CRP levels ($\geq$10 mg/l) was assessed from the time the CRP level was normalized to de-normalized ($\geq$10 mg/l).

The Kaplan—Meier method was used to estimate median and event-free rate of time-to-event endpoints, i.e. PFS, OS, and time from normalized to de-normalized CRP levels. Unstratified hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for time-to-event endpoints were calculated by the Cox proportional hazard model. Unstratified odds ratios for ORRs and corresponding 95% CIs were calculated by the logistic regression model.

Univariate analyses were conducted to explore the association of baseline characteristics, including baseline CRP levels and changes in CRP levels after initiation of treatment, with efficacy (ORR, PFS, and OS) in both arms. Baseline characteristics associated with the efficacy of avelumab plus axitinib were identified using multivariate analyses. This included clinically relevant variables that were not eliminated by covariate selection, such as age, number of International Metastatic RCC Database Consortium (IMDC) risk factors, number of target tumor sites, and CRP groups. Other variables investigated in univariate analyses were selected with a stepwise procedure; a two-sided *P* value had to be significant at the 0.15 level to enter the model, and *P* values within the model had to be significant at the 0.40 level in order to remain.

Individual IMDC risk groups, prior nephrectomy, sum of the longest diameter for target lesion at baseline, and time from histopathological diagnosis were not included in the multivariate model due to existence of multicollinearity; these factors correlated with the number of IMDC risk factors and the number of target tumor sites.

## RESULTS

### *Patients*

A total of 886 patients with aRCC were randomized to the avelumab plus axitinib ($n = 442$) and sunitinib arms ($n = 444$),[16] from which 393 and 396 patients, respectively, were included in the CRP analysis population. Baseline demographics and clinical characteristics were similar between the intention-to-treat and CRP analysis populations (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100564). In the avelumab plus axitinib arm, 234, 51, and 108 patients were classified into the normal, normalized, and non-normalized CRP groups, respectively; in the sunitinib arm, 232, 36, and 128 patients were classified into respective CRP groups (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100564). Median baseline CRP levels were 7.7 mg/l in the avelumab plus axitinib arm and 8.0 mg/l in the sunitinib arm.

### *Efficacy*

At data cut-off, minimum durations of follow-up for IA2 (cut-off date: 28 January 2019) and IA3 (cut-off date: 28 April 2020) were 13 and 28 months, respectively. In both the avelumab plus axitinib and sunitinib arms, ORR was favorable in the normal and normalized CRP groups versus the non-normalized CRP group (Figure 1A; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100564). In the normal, normalized, and non-normalized CRP groups in the avelumab plus axitinib arm, ORRs (95% CI) were 56.0% (49.4% to 62.4%), 66.7% (52.1% to 79.2%), and 45.4% (35.8% to 55.2%), with complete response (CR) rates of 3.8%, 11.8%, and 0.9%, respectively. In the respective CRP groups in the sunitinib arm, ORRs (95% CI) were 30.6% (24.7% to 37.0%), 41.7% (25.5% to 59.2%), and 19.5% (13.1% to 27.5%), with CR rates of 3.0%, 0%, and 1.6%.

PFS was longer in the normalized CRP group versus the normal CRP group in the avelumab plus axitinib arm but not in the sunitinib arm (Figure 1B). In the avelumab plus axitinib arm, median PFS (95% CI) was 15.2 months (12.5-21.0 months) in the normal CRP group, not reached (NR) [11.1 months-not estimable (NE)] in the normalized CRP group, and 7.0 months (5.6-9.9 months) in the non-normalized CRP group. Compared with the normal CRP group, the risk of progression or death was 28% lower in the normalized CRP group (unstratified HR, 0.724; 95% CI 0.453-1.156) and was 92% higher in the non-normalized CRP group (unstratified HR, 1.923; 95% CI 1.428-2.590). In the sunitinib arm, median PFS (95% CI) was 11.2 months in both the normal (8.4-13.9 months) and normalized (6.7-13.8 months) CRP groups and 4.2 months (2.8-5.6 months) in the non-normalized CRP group. Compared with the normal CRP group, the risk of progression or death was similar in the normalized CRP group (unstratified HR, 1.099; 95% CI 0.689-1.753) and was two times higher in the non-normalized CRP group (unstratified HR, 2.090; 95% CI 1.585-2.757). Kaplan—Meier curves for the normal and normalized CRP groups crossed at $\sim$12 months.

Additional analyses were conducted in the normalized CRP group to explore the difference between the avelumab plus axitinib and sunitinib arms. In both treatment arms, a higher increase in CRP levels was observed in patients with progressive disease (PD) than in patients with CR, partial response (PR), or stable disease (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100564). The median times from normalized CRP levels to de-normalized CRP levels ($\geq$10 mg/l) were 4.3 and 4.1 months in the avelumab plus axitinib and sunitinib arms, respectively (Figure 2). The risk of CRP deterioration from normalized to de-normalized was lower, however, with avelumab plus axitinib versus sunitinib (unstratified HR, 0.696; 95% CI 0.421-1.149).

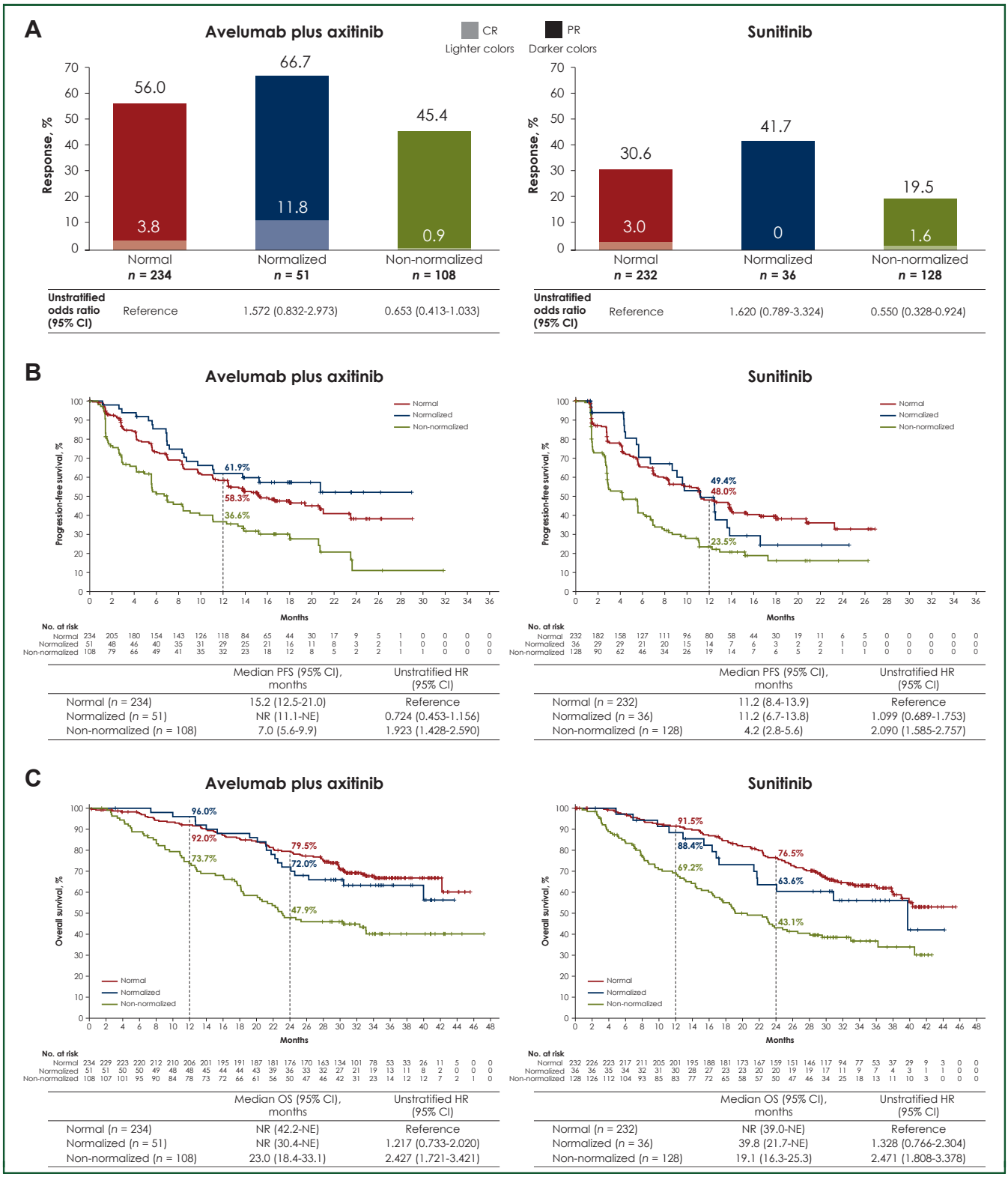


**Figure 1. Efficacy by changes in CRP levels.**

(A) ORR and CR rates per BICR assessment. Rates based on data from the IA2 (data cut-off date: 28 January 2019) are shown by changes in CRP levels.[a] (B) PFS per BICR assessment. PFS based on data from the IA2 (data cut-off date: 28 January 2019) are shown by changes in CRP levels.[a] (C) OS by changes in CRP levels. OS and CRP levels are based on data from the IA3 (data cut-off date: 28 April 2020).

BICR, blinded independent central review; CI, confidence interval; CR, complete response; CRP, C-reactive protein; HR, hazard ratio; IA2, second interim analysis; IA3, third interim analysis; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

[a]CRP groups were based on the data set from the IA3 (data cut-off date: 28 April 2020).

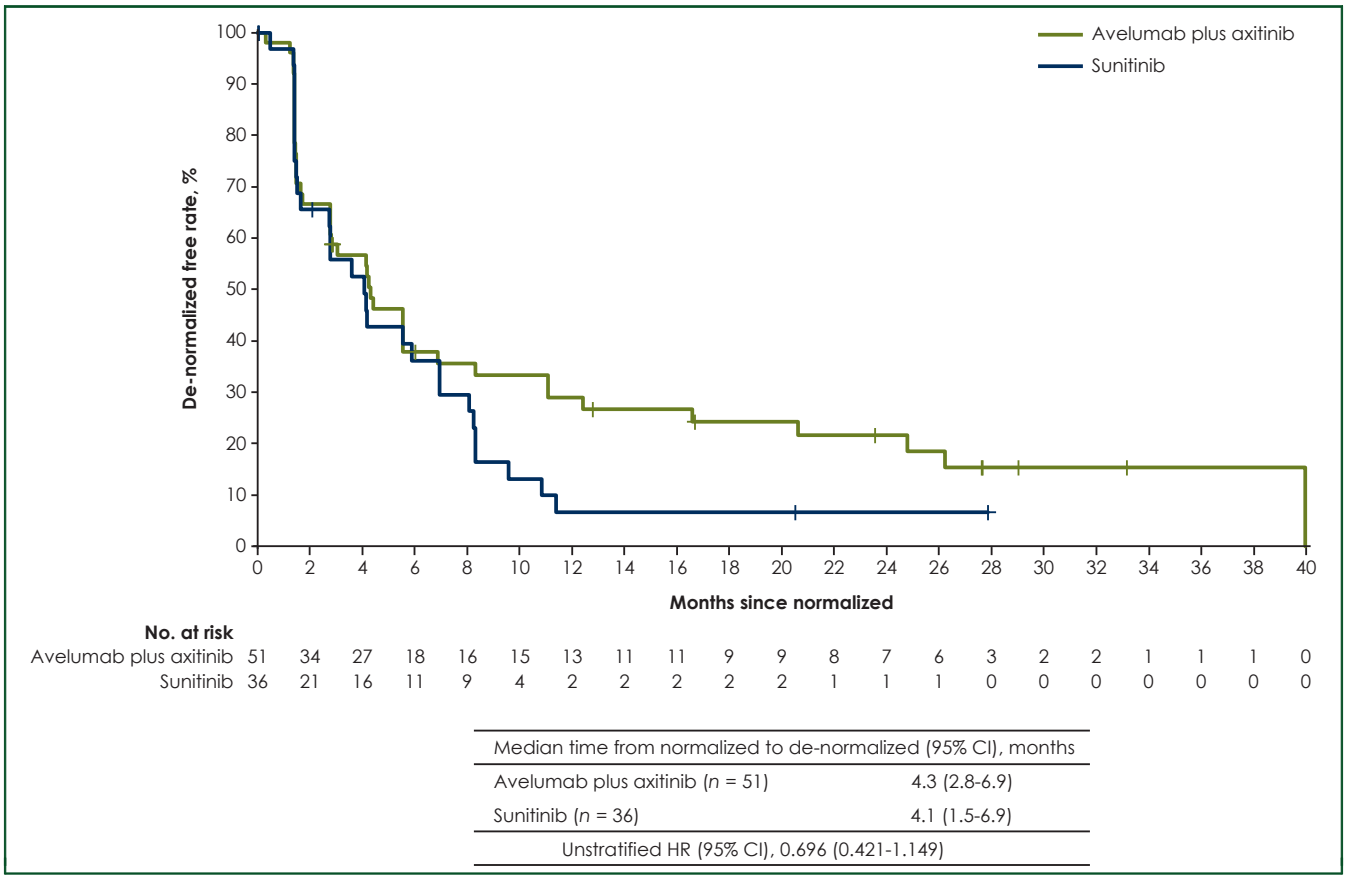


**Figure 2. Time to de-normalized CRP levels in patients in the normalized CRP group.**
CRP levels are based on data from the IA3 (data cut-off date: 28 April 2020).
CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IA3, third interim analysis.

In the avelumab plus axitinib arm, median OS (95% CI) was NR in the normal (42.2 months-NE) and normalized (30.4 months-NE) CRP groups and 23.0 months (18.4-33.1 months) in the non-normalized CRP group (Figure 1C). In the normal, normalized, and non-normalized CRP groups, 12-month OS rates were 92.0%, 96.0%, and 73.7%, and 24-month OS rates were 79.5%, 72.0%, and 47.9%, respectively. Compared with the normal CRP group, the risk of death was 22% higher in the normalized CRP group (unstratified HR, 1.217; 95% CI 0.733-2.020) and was more than two times higher in the non-normalized CRP group (unstratified HR, 2.427; 95% CI 1.721-3.421). In the sunitinib arm, median OS (95% CI) was NR (39.0 months-NE) in the normal CRP group, 39.8 months (21.7 months-NE) in the normalized CRP group, and 19.1 months (16.3-25.3 months) in the non-normalized CRP group. In the normal, normalized, and non-normalized CRP groups, 12-month OS rates were 91.5%, 88.4%, and 69.2%, and 24-month OS rates were 76.5%, 63.6%, and 43.1%, respectively. Compared with the normal CRP group, the risk of death was 33% higher in the normalized CRP group (unstratified HR, 1.328; 95% CI 0.766-2.304) and was more than two times higher in the non-normalized CRP group (unstratified HR, 2.471; 95% CI 1.808-3.378). OS data are still immature; follow-up for the final analysis is ongoing.

All efficacy outcomes were favorable with avelumab plus axitinib versus sunitinib in each CRP group.

Within the normal CRP group, ORR, PFS, and OS were similar in patients who had non-elevated CRP or elevated CRP during the 6-week avelumab plus axitinib treatment, whereas ORR and OS were more favorable in patients who had non-elevated CRP versus elevated CRP during the 6-week sunitinib treatment (Supplementary Table S3, Supplementary Figures S3 and S4, available at https://doi.org/10.1016/j.esmoop.2022.100564).

### *Baseline characteristics associated with efficacy in patients treated with avelumab plus axitinib*

Multivariate analyses for objective response showed that the odds of response were significantly higher in patients aged ≥65 to <75 years versus <65 years (odds ratio, 1.665; 95% CI 1.020-2.718; $P = 0.0414$) and in patients who were Asian versus White race (odds ratio, 2.095; 95% CI 1.118-3.925; $P = 0.0210$) (Table 1). The odds of response were significantly lower in patients with 2 (odds ratio, 0.500; 95% CI 0.260-0.959; $P = 0.0370$) and 3 (odds ratio, 0.329; 95% CI 0.124-0.874; $P = 0.0258$) IMDC risk factors than in those with no risk factors and in patients with 3 (odds ratio, 0.486; 95% CI 0.244-0.969; $P = 0.0404$) and ≥4 (odds ratio, 0.296;

**Table 1. Multivariate analysis for ORR per BICR assessment based on data from the IA2 (data cut-off date: 28 January 2019) in the avelumab plus axitinib arm**

| Baseline characteristics | Avelumab plus axitinib | | | |
|---|---|---|---|---|
| | *n* | CR + PR, *n* (%) | Odds ratio (95% CI) | *P* value[a] |
| **Age, years** | | | | |
| <65 | 271 | 134 (49.4) | Reference | |
| ≥65 to <75 | 138 | 84 (60.9) | 1.665 (1.020-2.718) | 0.0414 |
| ≥75 | 33 | 14 (42.4) | 0.797 (0.342-1.858) | 0.5993 |
| **Race** | | | | |
| White | 332 | 173 (52.1) | Reference | |
| Asian | 70 | 41 (58.6) | 2.095 (1.118-3.925) | 0.0210 |
| Others | 23 | 12 (52.2) | 1.016 (0.390-2.645) | 0.9740 |
| **No. of IMDC risk factors** | | | | |
| 0 | 94 | 63 (67.0) | Reference | |
| 1 | 157 | 90 (57.3) | 0.879 (0.484-1.599) | 0.6731 |
| 2 | 113 | 53 (46.9) | 0.500 (0.260-0.959) | 0.0370 |
| 3 | 44 | 14 (31.8) | 0.329 (0.124-0.874) | 0.0258 |
| 4-6 | 29 | 10 (34.5) | 0.391 (0.131-1.164) | 0.0916 |
| **CRP groups[b]** | | | | |
| Normal | 234 | 131 (56.0) | Reference | |
| Normalized | 51 | 34 (66.7) | 2.241 (1.096-4.580) | 0.0270 |
| Non-normalized | 108 | 49 (45.4) | 1.125 (0.625-2.023) | 0.6948 |
| **No. of target tumor sites (per BICR)** | | | | |
| 1 | 177 | 112 (63.3) | Reference | |
| 2 | 150 | 75 (50.0) | 0.611 (0.369-1.013) | 0.0562 |
| 3 | 69 | 29 (42.0) | 0.486 (0.244-0.969) | 0.0404 |
| ≥4 | 35 | 13 (37.1) | 0.296 (0.116-0.754) | 0.0107 |

BICR, blinded independent central review; CI, confidence interval; CR, complete response; CRP, C-reactive protein; IA2, second interim analysis; IA3, third interim analysis; IMDC, International Metastatic RCC Database Consortium; ORR, objective response rate; PR, partial response.
[a]Two-sided Wald $\chi^2$ test. *P* value in blue indicates <0.05.
[b]CRP groups were based on the data set from the IA3 (data cut-off date: 28 April 2020).

95% CI 0.116-0.754; $P = 0.0107$) target tumor sites compared with only 1 target tumor site. Compared with the normal CRP group, the odds of response was significantly higher in the normalized CRP group (odds ratio, 2.241; 95% CI 1.096-4.580; $P = 0.0270$) but not the non-normalized CRP group (odds ratio, 1.125; 95% CI 0.625-2.023; $P = 0.6948$).

Multivariate analyses for PFS showed that the risks of progression or death were significantly higher in patients with 1 (HR, 1.709; 95% CI 1.112-2.625; $P = 0.0144$), 3 (HR, 2.171; 95% CI 1.169-4.032; $P = 0.0141$), and 4-6 (HR, 2.483; 95% CI 1.274-4.836; $P = 0.0075$) IMDC risk factors versus no risk factors and in patients with ≥4 target tumor sites versus those with only 1 target tumor site (HR, 1.944; 95% CI 1.048-3.605; $P = 0.0349$) (Table 2). CRP level was a potential factor for the prediction of PFS; compared with the normal CRP group, HRs (95% CI) in the normalized and non-normalized CRP groups were 0.639 (0.390-1.044; $P = 0.0739$) and 1.390 (0.966-1.999; $P = 0.0760$), respectively.

Multivariate analyses for OS showed that the risk of death was significantly higher in patients with 1 (HR, 2.157; 95% CI 1.222-3.806; $P = 0.0080$), 2 (HR, 2.326; 95% CI 1.292-4.187; $P = 0.0049$), 3 (HR, 3.324; 95% CI 1.612-6.856; $P = 0.0011$), and 4-6 (HR, 3.654; 95% CI 1.669-7.998; $P = 0.0012$) IMDC risk factors versus no risk factors (Table 3). The risk of death was also significantly higher in patients with 2 (HR, 2.129; 95% CI 1.417-3.200; $P = 0.0003$) and 3 (HR, 1.827; 95% CI 1.094-3.052; $P = 0.0213$) target tumor sites versus only 1 target tumor site. Compared with the normal CRP group, the HR was not different in the normalized CRP group (0.990; 95% CI 0.582-1.683; $P = 0.9700$) but was significantly higher in the non-normalized CRP group (1.525; 95% CI 1.001-2.324; $P = 0.0496$).

Univariate analyses of baseline characteristics, including baseline CRP levels and changes in CRP levels, and association with ORR, PFS, and OS in both the avelumab plus axitinib and sunitinib arms are shown in Supplementary Tables S4-S6, available at https://doi.org/10.1016/j.esmoop.2022.100564.

## DISCUSSION

CRP is an important prognostic and predictive factor in patients with aRCC. CRP is an acute-phase protein and levels increase rapidly following interleukin-6 secretion by macrophages and T cells during infection, inflammation, and cancer.[27] In addition, RCC cells produce interleukin-6 and increased CRP levels in patients with RCC have been associated with changes in the tumor immune microenvironment and worse outcomes in previous studies.[36-39] The association between CRP and treatment efficacy in patients treated with an ICI plus a VEGFR inhibitor, however, has not been evaluated.

This follow-up study showed that baseline CRP levels and changes in CRP levels early after treatment were associated with clinical outcomes in patients with aRCC treated with avelumab plus axitinib. To our knowledge, this is the first report to explore the utility of the CRP level as a predictive marker for efficacy in patients with aRCC treated with an ICI plus a VEGFR inhibitor. The selected cut-off for the baseline CRP level of 10 mg/l was based on previous studies in

**Table 2. Multivariate analysis for PFS per BICR assessment based on data from the IA2 (data cut-off date: 28 January 2019) in the avelumab plus axitinib arm**

| Baseline characteristics | Avelumab plus axitinib | | | | |
|---|---|---|---|---|---|
| | *n* | No. of events, *n* (%) | Median PFS (95% CI), months | HR (95% CI) | *P* value[a] |
| **Age, years** | | | | | |
| <65 | 271 | 142 (52.4) | 11.6 (8.4-19.4) | Reference | |
| ≥65 to <75 | 138 | 72 (52.2) | 13.8 (11.1-18.0) | 0.922 (0.672-1.263) | 0.6117 |
| ≥75 | 33 | 15 (45.5) | 13.8 (7.0-NE) | 0.766 (0.416-1.410) | 0.3917 |
| **Sex** | | | | | |
| Male | 316 | 158 (50.0) | 13.9 (11.2-20.7) | Reference | |
| Female | 126 | 71 (56.3) | 9.9 (6.7-15.2) | 1.317 (0.953-1.818) | 0.0949 |
| **No. of IMDC risk factors** | | | | | |
| 0 | 94 | 34 (36.2) | 24.0 (20.7-NE) | Reference | |
| 1 | 157 | 87 (55.4) | 11.1 (8.5-15.2) | 1.709 (1.112-2.625) | 0.0144 |
| 2 | 113 | 61 (54.0) | 13.3 (7.0-23.6) | 1.530 (0.964-2.429) | 0.0714 |
| 3 | 44 | 26 (59.1) | 7.0 (2.8-13.9) | 2.171 (1.169-4.032) | 0.0141 |
| 4-6 | 29 | 19 (65.5) | 5.6 (1.8-9.0) | 2.483 (1.274-4.836) | 0.0075 |
| **CRP groups**[b] | | | | | |
| Normal | 234 | 112 (47.9) | 15.2 (12.5-21.0) | Reference | |
| Normalized | 51 | 21 (41.2) | NR (11.1-NE) | 0.639 (0.390-1.044) | 0.0739 |
| Non-normalized | 108 | 73 (67.6) | 7.0 (5.6-9.9) | 1.390 (0.966-1.999) | 0.0760 |
| **No. of target tumor sites (per BICR)** | | | | | |
| 1 | 177 | 85 (48.0) | 16.1 (11.6-NE) | Reference | |
| 2 | 150 | 79 (52.7) | 12.5 (8.3-18.0) | 1.327 (0.902-1.952) | 0.1514 |
| 3 | 69 | 42 (60.9) | 9.7 (5.7-15.2) | 1.344 (0.833-2.168) | 0.2253 |
| ≥4 | 35 | 19 (54.3) | 6.8 (2.7-NE) | 1.944 (1.048-3.605) | 0.0349 |
| **Lung only (target tumor, per BICR)** | | | | | |
| Yes | 50 | 29 (58.0) | 12.5 (7.0-20.8) | Reference | |
| No | 392 | 200 (51.0) | 13.4 (11.0-16.1) | 0.682 (0.421-1.104) | 0.1192 |

BICR, blinded independent central review; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IA2, second interim analysis; IA3, third interim analysis; IMDC, International Metastatic RCC Database Consortium; NE, not estimable; NR, not reached; PFS, progression-free survival.
[a]Two-sided Wald $\chi^2$ test. *P* value in blue indicates <0.05.
[b]CRP groups were based on the data set from the IA3 (data cut-off date: 28 April 2020).

patients with metastatic RCC.[32,34,35] This cut-off was reasonable given that median baseline CRP levels were 7.7 mg/l and 8.0 mg/l in the avelumab plus axitinib and sunitinib arms, respectively. Early changes in CRP levels after initiation of nivolumab treatment have been associated with efficacy in patients with aRCC.[32,33] Therefore, CRP levels within 6 weeks after initiation of treatment were analyzed in the current study.

**Table 3. Multivariate analysis for OS based on data from the IA3 (data cut-off date: 28 April 2020) in the avelumab plus axitinib arm**

| Baseline characteristics | Avelumab plus axitinib | | | | | | |
|---|---|---|---|---|---|---|---|
| | *n* | No. of events, *n* (%) | Median OS (95% CI), months | Event-free rate (95% CI), % | | HR (95% CI) | *P* value[a] |
| | | | | 12 months | 24 months | | |
| **Age, years** | | | | | | | |
| <65 | 271 | 104 (38.4) | NR (42.2-NE) | 84.5 (79.6-88.4) | 69.7 (63.7-74.8) | Reference | |
| ≥65 to <75 | 138 | 54 (39.1) | NR (30.4-NE) | 87.0 (79.9-91.7) | 66.7 (57.8-74.1) | 1.193 (0.826-1.724) | 0.3463 |
| ≥75 | 33 | 14 (42.4) | 32.6 (23.0-NE) | 90.5 (73.3-96.8) | 69.8 (49.9-83.1) | 1.159 (0.612-2.197) | 0.6503 |
| **No. of IMDC risk factors** | | | | | | | |
| 0 | 94 | 17 (18.1) | NR (NE-NE) | 95.7 (88.9-98.4) | 83.7 (74.4-89.8) | Reference | |
| 1 | 157 | 58 (36.9) | NR (40.0-NE) | 89.5 (83.5-93.4) | 71.6 (63.7-78.1) | 2.157 (1.222-3.806) | 0.0080 |
| 2 | 113 | 53 (46.9) | 32.6 (29.7-NE) | 85.4 (77.3-90.8) | 66.5 (56.7-74.6) | 2.326 (1.292-4.187) | 0.0049 |
| 3 | 44 | 24 (54.5) | 24.7 (11.9-NE) | 65.9 (49.3-78.2) | 53.7 (37.4-67.4) | 3.324 (1.612-6.856) | 0.0011 |
| 4-6 | 29 | 18 (62.1) | 19.9 (9.6-NE) | 59.9 (39.3-75.4) | 37.4 (19.9-55.0) | 3.654 (1.669-7.998) | 0.0012 |
| **CRP groups** | | | | | | | |
| Normal | 234 | 71 (30.3) | NR (42.2-NE) | 92.0 (87.7-94.9) | 79.5 (73.6-84.2) | Reference | |
| Normalized | 51 | 19 (37.3) | NR (30.4-NE) | 96.0 (84.9-99.0) | 72.0 (57.4-82.4) | 0.990 (0.582-1.683) | 0.9700 |
| Non-normalized | 108 | 61 (56.5) | 23.0 (18.4-33.1) | 73.7 (64.2-81.0) | 47.9 (38.1-57.1) | 1.525 (1.001-2.324) | 0.0496 |
| **No. of target tumor sites (per BICR)** | | | | | | | |
| 1 | 177 | 48 (27.1) | NR (42.2-NE) | 93.7 (88.9-96.4) | 80.9 (74.2-86.0) | Reference | |
| 2 | 150 | 68 (45.3) | 40.0 (25.3-NE) | 82.9 (75.6-88.2) | 62.8 (54.2-70.2) | 2.129 (1.417-3.200) | 0.0003 |
| 3 | 69 | 37 (53.6) | 26.3 (19.9-NE) | 75.0 (62.8-83.6) | 52.4 (39.9-63.5) | 1.827 (1.094-3.052) | 0.0213 |
| ≥4 | 35 | 16 (45.7) | 30.4 (21.2-NE) | 79.0 (60.9-89.4) | 63.3 (44.5-77.3) | 1.913 (1.000-3.663) | 0.0502 |

BICR, blinded independent central review; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IA3, third interim analysis; IMDC, International Metastatic RCC Database Consortium; NE, not estimable; NR, not reached; OS, overall survival.
[a]Two-sided Wald $\chi^2$ test. *P* value in blue indicates <0.05.

Efficacy outcomes in the normal and normalized CRP groups were favorable versus those in the non-normalized CRP group in both arms. This indicates that not only patients with low baseline CRP levels benefit from treatment, but also that those with high baseline CRP levels can benefit if their CRP levels decrease during treatment. Similar results were observed in patients with metastatic RCC treated with nivolumab in a two-center study, in which patients with normal (low CRP at baseline and 1 month after treatment) and normalized (high CRP at baseline and low CRP 1 month after treatment) CRP levels showed significantly better immune-related PFS than those with non-normalized (high CRP at baseline and 1 month after treatment) CRP levels.[33]

In both the avelumab plus axitinib and sunitinib arms, response rates were favorable in the normalized CRP group versus the normal and non-normalized CRP groups. In the avelumab plus axitinib arm, response rates in the normalized CRP group (ORR, 66.7%; CR rate, 11.8%) were higher than those reported in the overall patient population of the JAVELIN Renal 101 trial (ORR, 52.5%; CR rate, 3.8%).[20] A similar trend was observed in a retrospective study of patients with metastatic RCC treated with second- or later-line nivolumab, in which the ORR and CR rate were higher in the normalized CRP group than in the normal and non-normalized CRP groups.[32]

Median PFS was longer in the normalized CRP group (NR) versus the normal CRP group (15.2 months) in the avelumab plus axitinib arm. A similar trend for PFS was observed in patients with metastatic RCC treated with second- or later-line nivolumab, where median PFS was longer in the normalized CRP group (8.38 months) versus the normal (6.28 months) or non-normalized (2.33 months) CRP groups.[32] This trend for PFS, however, was not observed in the sunitinib arm in our study, with the Kaplan—Meier curves for the normal and normalized CRP groups crossing at ~12 months. The different trends observed in the two arms were explored further. In both arms, CRP levels during the post-treatment tumor assessment in the normalized CRP group were higher in patients with PD than in patients with CR, PR, or stable disease. The risk of CRP deterioration from normalized to de-normalized, however, was lower in the avelumab plus axitinib arm versus the sunitinib arm, indicating that maintaining CRP levels during treatment, in addition to early CRP response, may be a key factor in controlling tumor growth and avoiding progression. This may partially explain the favorable efficacy with avelumab plus axitinib versus sunitinib and the worsening PFS after 12 months in the sunitinib arm in the normalized CRP group. Similarly, a study in patients with metastatic RCC treated with TKIs found that the Kaplan—Meier curves for PFS crossed between non-elevated and early CRP responder groups.[30]

Median OS was NR in the normal and normalized CRP groups in the avelumab plus axitinib arm; OS data are still immature, and follow-up for final analyses are ongoing. No substantial differences were observed in OS between the normalized and normal CRP groups in the avelumab plus axitinib arm. The OS trend for these two groups inverted after 2 years of treatment, which might be explained by the prognostic characteristics of patients. Specifically, the 10 patients who died between 18 and 26 months after start of treatment in the normalized CRP group had worse prognostic characteristics than patients who died between 18 and 26 months after start of treatment in the normal or non-normalized CRP groups (higher proportion with 2-6 IMDC risk factors and $\geq$3 target tumors sites; data not shown). The potential for further exploration of this observation is limited, however, by the small number of patients in the normalized CRP group in the avelumab plus axitinib arm ($n = 51$) and immaturity of the OS data, and the potential influence of treatments received following PD, cannot be excluded. In the sunitinib arm, OS was shorter in the normalized CRP group versus the normal CRP group. Median OS was shorter in the non-normalized CRP group versus the normal or normalized CRP groups in both treatment arms. This finding suggests that non-normalized CRP levels are a poor prognostic factor regardless of study treatment. In patients with metastatic RCC treated with second- or later-line nivolumab, median OS was shorter in the normalized CRP group (26.0 months) versus the normal CRP group (NR). In addition, median OS was shortest in the non-normalized CRP group (8.02 months).[32] A similar OS trend was observed in patients with metastatic RCC treated with a TKI.[30]

Interestingly, in the normal CRP group, all efficacy endpoints were similar in patients with non-elevated CRP versus elevated CRP in the avelumab plus axitinib arm. This finding suggests that baseline normal CRP is a prognostic marker regardless of CRP levels after treatment.

Consistent with the results in the overall patient population,[16,20] all efficacy outcomes investigated in the current analyses favored avelumab plus axitinib versus sunitinib within each CRP group. Multivariate analyses showed that normalized or non-normalized CRP levels were independent factors for the prediction of ORR or OS, respectively, with avelumab plus axitinib. In addition, normalized or non-normalized CRP levels were potential factors for the prediction of PFS with avelumab plus axitinib. The multivariate analyses also suggest that baseline CRP levels and early changes in CRP levels during treatment may be predictive markers for the efficacy of ICI plus VEGFR inhibitor therapy in patients with aRCC. Previous studies also suggest that baseline CRP and early changes in CRP levels during treatment are predictive markers for the efficacy of ICIs[31-33] as well as TKIs.[23-30]

Our study has some limitations. The sample size of patients in the normalized CRP group in the JAVELIN Renal 101 trial is small, with only 51 patients in the avelumab plus axitinib arm and 36 patients in the sunitinib arm. In addition, the OS data were still immature at IA3; follow-up for the final analysis is ongoing. Across all analyses, CRP groups were categorized using CRP levels after treatment, which could cause lead-time bias. The potential for bias was considered limited, however, because CRP levels assessed during early treatment (6 weeks) were analyzed, and the tumor assessment at 6 weeks after initiation of treatment was the first preplanned tumor assessment in our study.

In conclusion, the results from this study suggest that baseline CRP levels and early changes in CRP levels during treatment may be used as predictive markers for the efficacy of avelumab plus axitinib in patients with aRCC. Although ICI combination therapies have greatly improved treatment outcomes for patients with aRCC, not all patients benefit. Potential strategies to improve patient outcomes that are being explored in other studies include improving drug delivery methods, use of state-of-the-art sequencing methods, and increasing the characterization of molecular drivers of variant histology.[40] In addition, novel therapeutic approaches are currently being explored in patients with aRCC.[41,42]

### *Conclusions*

Exploratory analyses from the JAVELIN Renal 101 suggest that CRP levels at baseline and early after treatment may predict efficacy with avelumab plus axitinib in patients with aRCC.

## ACKNOWLEDGEMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers, as well as Mana Aizawa of Pfizer R&D Japan for data analysis. Medical writing support was provided by Kakoli Parai of ClinicalThinking and was funded by Pfizer and Merck (CrossRef Funder ID: 10.13039/100009945).

## FUNDING

This work was supported by Pfizer (no grant number) as part of an alliance between Pfizer and Merck (CrossRef Funder ID: 10.13039/100009945). Both companies provided the trial drugs and worked with investigators to design the study; collect, analyze, and interpret the data; and prepare the manuscript.

## 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 for Novartis, Ono Pharmaceutical, and Taiho Pharmaceutical; and has received research funding from Pfizer, Ono Pharmaceutical, Takeda, Astellas Pharma, AstraZeneca, Novartis, Chugai Pharma, MSD, and Eisai. JLhas received personal fees from Eisai, GlaxoSmithKline, Kymab, Roche/Genentech, Secarna, Pierre Fabre, and EUSA Pharma, and has received grants and personal fees from MSD, Pfizer, and Novartis. BVhas served in a consulting or advisory role for Pfizer, Merck, Ipsen, and MSD; has provided speaker services for MSD, Ipsen, and EUSA Pharma; has received honoraria from Pfizer, Bristol Myers Squibb, and EUSA Pharma; and has received research funding from Pfizer, Merck, Calithera Biosciences, and MSD. JHhas served in a consulting or advisory role for Achilles Therapeutics, AIMM Therapeutics, Bristol Myers Squibb, Immunocore, Ipsen, MSD, Neogene Therapeutics, Neon Therapeutics, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, and Third Rock Ventures, and has received research funding from Amgen, Bristol Myers Squibb, MSD, Neon Therapeutics, and Novartis. HK has received research funding from Taiho Pharmaceutical, Takeda, MSD, Astellas Pharma, Ono Pharmaceutical, Nihon Medi-Physics, Fujifilm, and Kissei Pharmaceutical. ME has served in a consulting or advisory role for Pfizer, Eisai, Ono Pharmaceutical, AstraZeneca, Chugai Pharma, Olympus, Johnson & Johnson, Bristol Myers Squibb, and Merck; has provided speaker services for MSD, Ono Pharmaceutical, Chugai Pharma, Novartis, Pfizer, Bristol Myers Squibb, Takeda, and Janssen; and has received research funding from Kissei Pharmaceutical, Sanofi, Astellas Pharma, Ono Pharmaceutical, Takeda, and Bayer. M-OG has served in a consulting or advisory role for AstraZeneca, Bristol Myers Squibb, Ipsen, MSD, Ono Pharmaceutical, Pfizer, Astellas Pharma, and EUSA Pharma; has received travel and accommodations expenses from Bristol Myers Squibb and Merck; has received honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Medac, MSD, Ono Pharmaceutical, Novartis, Pfizer, Ipsen, Merck, and EUSA Pharma; and has received research funding from Bristol Myers Squibb and Intuitive Surgical. YF is an employee of Pfizer R&D Japan G. K. YU is an employee of Pfizer R&D Japan G. K. and also holds Pfizer stock. BH is an employee of Pfizer. MM is an employee of Pfizer. AdP is an employee of Pfizer and also holds Pfizer stock. TKC has received support for the present manuscript from Pfizer and Merck; has received institutional research funding from AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Eisai, Exelixis, GlaxoSmithKline, Lilly, MSD, Nikang, Novartis, Pfizer, Roche, Sanofi/Aventis, Takeda, and Merck; holds patents, royalties, and other intellectual properties related to biomarkers of immune checkpoint blockers and ctDNA; has served in a consulting role or received honoraria from Alexion, Analysis Group, Aravive, AstraZeneca, Aveo, Bayer, Bristol Myers Squibb, Calithera, Cerulean, Corvus, Eisai, Exelixis, Foundation Medicine, Genentech, GlaxoSmithKline, Heron Therapeutics, Infinity Pharma, Ipsen, IQVIA, Janssen Oncology, Lilly, MSD, National Comprehensive Cancer Network, NiKang, Novartis, Nuscan, Peloton, Pfizer, Prometheus, Roche, Sanofi/Aventis, Surface Oncology, Tempest, Merck, and UpToDate; has served in CME-related events for OncLive, PVI, and MJH Life Sciences; is member of the National Cancer Institute Genitourinary Steering Committee, ASCO, ESMO, and National Comprehensive Cancer Network; has received travel expenses for meetings, lectures, and advisory boards; and holds stock with Pionyr and Tempest.

## 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.

## REFERENCES


1. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. *N Engl J Med*. 2017;376(4):354-366.
2. Bukowski RM. Third generation tyrosine kinase inhibitors and their development in advanced renal cell carcinoma. *Front Oncol*. 2012;2:13.
3. Ross K, Jones RJ. Immune checkpoint inhibitors in renal cell carcinoma. *Clin Sci*. 2017;131(21):2627-2642.
4. Carlo MI, Voss MH, Motzer RJ. Checkpoint inhibitors and other novel immunotherapies for advanced renal cell carcinoma. *Nat Rev Urol*. 2016;13(7):420-431.
5. Boyerinas B, Jochems C, Fantini M, et al. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (MSB0010718C) on human tumor cells. *Cancer Immunol Res*. 2015;3(10):1148-1157.
6. Vaishampayan U, Schöffski P, Ravaud A, et al. Avelumab monotherapy as first-line or second-line treatment in patients with metastatic renal cell carcinoma: phase Ib results from the JAVELIN Solid Tumor trial. *J Immunother Cancer*. 2019;7(1):275.
7. Inlyta (axitinib). Prescribing information. Pfizer Laboratories Div Pfizer Inc; 2020.
8. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.
9. Ueda T, Uemura H, Tomita Y, et al. Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from the global randomized Phase 3 AXIS trial. *Jpn J Clin Oncol*. 2013;43(6):616-628.
10. Tomita Y, Uemura H, Fujimoto H, et al. Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: a phase II study in Japanese patients with cytokine-refractory metastatic renal cell Carcinoma. *Eur J Cancer*. 2011;47(17):2592-2602.
11. Eto M, Uemura H, Tomita Y, et al. Overall survival and final efficacy and safety results from a Japanese phase II study of axitinib in cytokine-refractory metastatic renal cell carcinoma. *Cancer Sci*. 2014;105(12):1576-1583.
12. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol*. 2013;14(13):1287-1294.
13. Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol*. 2013;14(12):1233-1242.
14. Tomita Y, Fukasawa S, Oya M, et al. Key predictive factors for efficacy of axitinib in first-line metastatic renal cell carcinoma: subgroup analysis in Japanese patients from a randomized, double-blind phase II study. *Jpn J Clin Oncol*. 2016;46(11):1031-1041.
15. Oya M, Tomita Y, Fukasawa S, et al. Overall survival of first-line axitinib in metastatic renal cell carcinoma: Japanese subgroup analysis from phase II study. *Cancer Sci*. 2017;108(6):1231-1239.
16. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1103-1115.
17. Bavencio (avelumab). Prescribing information. Rockland, MA: EMD Serono, Inc. and Pfizer Inc.
18. European Medicines Agency. Bavencio. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/bavencio. Accessed November 5, 2021.
19. Pharmaceuticals and Medical Devices Agency. New drugs approved in FY 2019. Available at https://www.pmda.go.jp/files/000235289.pdf. Accessed August 18, 2022.
20. Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol*. 2020;31(8):1030-1039.
21. Bromwich E, McMillan DC, Lamb GW, Vasey PA, Aitchison M. The systemic inflammatory response, performance status and survival in patients undergoing alpha-interferon treatment for advanced renal cancer. *Br J Cancer*. 2004;91(7):1236-1238.
22. Casamassima A, Picciariello M, Quaranta M, et al. C-reactive protein: a biomarker of survival in patients with metastatic renal cell carcinoma treated with subcutaneous interleukin-2 based immunotherapy. *J Urol*. 2005;173(1):52-55.
23. Yasuda Y, Saito K, Yuasa T, et al. Prognostic impact of pretreatment C-reactive protein for patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. *Int J Clin Oncol*. 2013;18(5):884-889.
24. Beuselinck B, Vano YA, Oudard S, et al. Prognostic impact of baseline serum C-reactive protein in patients with metastatic renal cell carcinoma (RCC) treated with sunitinib. *BJU Int*. 2014;114(1):81-89.
25. Teishima J, Kobatake K, Kitano H, et al. The impact of change in serum C-reactive protein level on the prediction of effects of molecular targeted therapy in patients with metastatic renal cell carcinoma. *BJU Int*. 2016;117(6B):E67-E74.
26. Teishima J, Kobatake K, Shinmei S, et al. The effect of kinetics of C-reactive protein in the prediction of overall survival in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitor. *Urol Oncol*. 2017;35(11):662.e1-662.e7.
27. Pilskog M, Beisland C, Akslen LA, et al. Predictive value of C-reactive protein in patients treated with sunitinib for metastatic clear cell renal cell carcinoma. *BMC Urol*. 2017;17(1):74.
28. Fujita T, Tabata KI, Ishii D, Matsumoto K, Yoshida K, Iwamura M. Prognostic effect of serum C-reactive protein kinetics on advanced renal cell carcinoma treated with sunitinib. *Mol Clin Oncol*. 2017;6(5):691-696.
29. Takamatsu K, Mizuno R, Omura M, et al. Prognostic value of baseline serum C-reactive protein level in intermediate-risk group patients with metastatic renal-cell carcinoma treated by first-line vascular endothelial growth factor-targeted therapy. *Clin Genitourin Cancer*. 2018;16(4):e927-e933.
30. Yasuda Y, Saito K, Yuasa T, et al. Early response of C-reactive protein as a predictor of survival in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. *Int J Clin Oncol*. 2017;22(6):1081-1086.
31. Marshall MA, Ribas A, Huang B. Evaluation of baseline serum C-reactive protein (CRP) and benefit from tremelimumab compared to chemotherapy in first-line melanoma. *J Clin Oncol*. 2010;28(suppl 15):2609.
32. Ishihara H, Takagi T, Kondo T, et al. Predictive impact of an early change in serum C-reactive protein levels in nivolumab therapy for metastatic renal cell carcinoma. *Urol Oncol*. 2020;38(5):526-532.
33. Noguchi G, Nakaigawa N, Umemoto S, et al. C-reactive protein at 1 month after treatment of nivolumab as a predictive marker of efficacy in advanced renal cell carcinoma. *Cancer Chemother Pharmacol*. 2020;86(1):75-85.
34. Ramsey S, Lamb GW, Aitchison M, Graham J, McMillan DC. Evaluation of an inflammation-based prognostic score in patients with metastatic renal cancer. *Cancer*. 2007;109(2):205-212.
35. Naito S, Kinoshita H, Kondo T, et al. Prognostic factors of patients with metastatic renal cell carcinoma with removed metastases: a multicenter study of 556 patients. *Urology*. 2013;82(4):846-851.
36. Miki S, Iwano M, Miki Y, et al. Interleukin-6 (IL-6) functions as an in vitro autocrine growth factor in renal cell carcinomas. *FEBS Lett*. 1989;250(2):607-610.
37. Koo AS, Armstrong C, Bochner B, et al. Interleukin-6 and renal cell cancer: production, regulation, and growth effects. *Cancer Immunol Immunother*. 1992;35(2):97-105.
38. Nakayama T, Saito K, Kumagai J, et al. Higher serum C-reactive protein level represents the immunosuppressive tumor microenvironment in patients with clear cell renal cell carcinoma. *Clin Genitourin Cancer*. 2018;16(6):e1151-e1158.
39. O'Brian D, Prunty M, Hill A, Shoag J. The role of C-reactive protein in kidney, bladder, and prostate cancers. *Front Immunol*. 2021;12:721989.
40. Choueiri TK, Atkins MB, Bakouny Z, et al. Summary from the first Kidney Cancer Research Summit, September 12—13, 2019: a focus on translational research. *J Natl Cancer Inst*. 2021;113(3):234-243.

41. Ravi P, Bakouny Z, Schmidt A, Choueiri TK. Novel therapeutic approaches and the evolution of drug development in advanced kidney cancer. *Cancer J*. 2020;26(5):464-470.

42. Braun DA, Bakouny Z, Hirsch L, et al. Beyond conventional immune-checkpoint inhibition — novel immunotherapies for renal cell carcinoma. *Nat Rev Clin Oncol*. 2021;18(4):199-214.