BMJ Oncology

Association between neutrophil-to-eosinophil ratio and efficacy outcomes with avelumab plus axitinib or sunitinib in patients with advanced renal cell carcinoma: post hoc analyses from the JAVELIN Renal 101 trial

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To cite: Tucker M, Chen Y-W, Voss MH, *et al*. Association between neutrophil-to-eosinophil ratio and efficacy outcomes with avelumab plus axitinib or sunitinib in patients with advanced renal cell carcinoma: post hoc analyses from the JAVELIN Renal 101 trial. *BMJ Oncology* 2024;**3**:e000181. doi:10.1136/bmjonc-2023-000181

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjonc-2024-000481).

Received 30 August 2023
Accepted 12 May 2024

Linked

► https://doi.org/10.1136/bmjonc-2024-000481

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ABSTRACT

Objective We report post hoc analyses of efficacy with first-line avelumab plus axitinib or sunitinib according to baseline neutrophil-to-eosinophil ratio (NER) in patients with advanced renal cell carcinoma (aRCC) from the JAVELIN Renal 101 phase 3 trial.

Methods and analysis Progression-free survival (PFS), overall survival (OS) and objective response per baseline NER were analysed in the overall population and in patients with programmed death ligand 1 (PD-L1+) tumours. Multivariable Cox regression analyses to assess the effect of NER after adjustment for other baseline variables were conducted.

Results In NER <median versus ≥median subgroups of the avelumab plus axitinib arm, HRs for PFS and OS were 0.81 (95% CI 0.630 to 1.035) and 0.67 (95% CI 0.481 to 0.940), and objective response rates (ORRs) were 63.9% vs 55.2%, respectively. The HR for PFS in the PD-L1+ subgroup was 0.72 (95% CI 0.520 to 0.986). Comparing NER-defined subgroups in the sunitinib arm, HRs for PFS and OS were 0.93 (95% CI 0.728 to 1.181) and 0.57 (95% CI 0.424 to 0.779), and ORRs were 32.8% versus 30.8%, respectively. Within NER subgroups, analyses of PFS, OS and ORR favoured avelumab plus axitinib versus sunitinib treatment. Interaction tests that assessed the association between treatment and NER yielded conflicting results when NER was assessed as a dichotomised variable (median cut-off) or continuous variable.

Conclusion Hypothesis-generating analyses suggest that baseline NER may be prognostic for longer OS irrespective of treatment. Analyses of the association between NER level and treatment outcomes with avelumab plus axitinib versus sunitinib were inconclusive.

Trial registration number NCT02684006.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A lower baseline neutrophil-to-eosinophil ratio (NER) has been associated with improved efficacy of first-line nivolumab plus ipilimumab in patients with advanced renal cell carcinoma (aRCC).

⇒ In the phase 3 JAVELIN Renal 101 trial, first-line avelumab plus axitinib significantly improved progression-free survival and objective response rate compared with sunitinib in patients with aRCC; however, the relationship between NER and clinical outcomes is unknown.

WHAT THIS STUDY ADDS

⇒ In this post hoc analysis from the JAVELIN Renal 101 trial, baseline NER <median appeared to be prognostic for longer overall survival irrespective of treatment.

⇒ Analyses that assessed the relationship between NER level and treatment outcomes were inconclusive but suggested a stronger association for avelumab plus axitinib versus sunitinib, particularly in patients with PD-L1+ tumours.

⇒ All analyses reported are exploratory and were performed for hypothesis-generating purposes only.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further evaluation of NER as a potential biomarker in patients with aRCC receiving immune checkpoint inhibitor-based combination treatment is needed.

INTRODUCTION

Immune checkpoint inhibitor (ICI)-based combinations are standard first-line (1L) treatment for patients with advanced renal cell carcinoma (aRCC), and several combinations have been approved.[1 2] Identification of reliable predictive and prognostic biomarkers may enable more individualised treatment for patients with aRCC.[3] The

most commonly used prognostic model for aRCC is the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) classification, which uses 6 factors (time interval from diagnosis to treatment, Karnofsky performance status, haemoglobin level, platelet count, neutrophil count and serum calcium concentration) to categorise patients into risk groups.[4] The predictive and prognostic value of various biomarkers has been explored in aRCC, including programmed death ligand 1 (PD-L1) expression, genomic alterations, gene expression signatures and peripheral blood biomarkers.[3 5]

Given the link between inflammation and the pathogenesis and progression of cancer, inflammatory biomarkers have been a focus of research for ICI-based treatment regimens.[6–8] Various studies in solid tumours have found that levels or ratios of different types of blood cells including platelet-to-lymphocyte, lymphocyte-to-monocyte, neutrophil-to-lymphocyte and neutrophil-to-eosinophil ratios (NERs) are associated with efficacy outcomes in patients receiving ICI-based therapy.[9–17] Clinical data from patients with metastatic RCC suggest that an increase in eosinophil levels during treatment may be prognostic for response to ICIs or tyrosine kinase inhibitor (TKIs).[18 19] In a recent study, a lower baseline NER was associated with improved clinical outcomes in patients with aRCC treated with 1L nivolumab plus ipilimumab.[20] Observations were similar in retrospective studies of patients with metastatic RCC who received various ICI-based regimens or who received nivolumab as second-line or later treatment.[21 22] Preclinical studies suggest that eosinophil activation regulates macrophage polarisation and promotes CD8+ T cell recruitment and response to ICIs.[23–25] Further analyses of NER as a predictive marker in patients with aRCC receiving 1L ICI plus TKI treatment, including comparisons with other treatment regimens, are required.

In the phase 3 JAVELIN Renal 101 trial (NCT02684006), 1L treatment with avelumab, a fully human anti-PD-L1 monoclonal antibody, plus axitinib, a selective antiangiogenic TKI, significantly improved progression-free survival (PFS) and the objective response rate (ORR) in patients with aRCC compared with sunitinib, an antiangiogenic TKI therapy that was the prior 1L standard of care.[26 27] Exploratory analyses have shown that various genomic and transcriptomic biomarker signatures, in addition to C reactive protein levels, can predict efficacy outcomes with avelumab plus axitinib but not sunitinib, whereas neutrophil-to-lymphocyte ratio (NLR) was prognostic and associated with outcomes for both treatment regimens.[17 28 29] The potential for NER to serve as a prognostic or predictive biomarker for 1L avelumab plus axitinib treatment in comparison with sunitinib has not been assessed. In the exploratory analyses reported here, we assessed the association between baseline NER and efficacy outcomes in the avelumab plus axitinib and sunitinib arms of the JAVELIN Renal 101 trial.

METHODS

Study design and participants

JAVELIN Renal 101 is an ongoing phase 3, multicentre, randomised, open-label study comparing 1L avelumab plus axitinib versus sunitinib in patients with aRCC.[26] Full details of the trial design have been reported previously.[26] Briefly, eligible participants were adults with previously untreated aRCC with a clear-cell component, ≥1 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. All participating patients provided written informed consent. Patients and the public were not involved in the design, conduct, reporting or dissemination of this research. Avelumab was administered at 10 mg/kg of body weight as a 1-hour intravenous infusion every 2 weeks in 6-week cycles. Axitinib was taken orally at a starting dose of 5 mg two times a day in a continuous dosing schedule. Sunitinib was taken orally at 50 mg one time a day for 4 weeks of 6-week cycles.

Assessments

The 2 primary endpoints of JAVELIN Renal 101 are PFS per RECIST version 1.1 according to blinded independent central review (BICR) and overall survival (OS) in patients with PD-L1+ tumours (≥1% of immune cells staining positive within the tumour area of the tested tissue sample).[26] PD-L1 expression was assessed at a central laboratory using the Ventana PD-L1 (SP263) assay (Ventana Medical Systems). Key secondary endpoints are PFS by BICR according to RECIST 1.1 and OS in the overall population. Other secondary endpoints include PFS by investigator assessment and objective response. In this report, all analyses of PFS and objective response were based on investigator assessment.

NER was calculated as the absolute count of neutrophils (per nL) divided by the absolute count of eosinophils (per nL). NER values were gathered from the last blood test within 28 days before the administration of study treatment. Patients with non-missing neutrophil and eosinophil values at baseline were included in the analysis set; baseline eosinophil values of 0 were imputed to 0.01.

Translational analysis

The volcano plot comparing gene expression profiles for patients with NER <median and NER ≥median was generated as previously described using a Cox proportional hazards model.[28] Two-sided Wald test was used for p values and $-\log_{10}$(p value) was used for visualisation. In addition to the individual differential gene expression analyses, previously reported gene expression signatures were also evaluated.[28 30–32] Gene expression signatures were calculated using the mean aggregated individual gene expression values per sample. The median was calculated and used to stratify patients as having gene expression signatures >median or ≤median. The Cox proportional

hazards model was used to evaluate patient subgroups, as previously described.[28]

Statistical analyses

Prespecified statistical analyses for the JAVELIN Renal 101 trial have been reported previously.[26] Analyses reported here are based on the preplanned third interim analysis for OS (28 April 2020), which was performed when approximately 336 PFS events by BICR had occurred in patients with PD-L1+ tumours and 15 months after the final analysis for PFS (≥12 months of follow-up in all randomised patients). In post hoc analyses, median NER was determined for all randomised patients, and NER was dichotomised by NER <median or NER ≥median. The median NER in each arm was used to define NER subgroups when comparing outcomes between NER subgroups within the avelumab plus axitinib or sunitinib arm. However, the median NER in the overall population was used to define NER subgroups when comparing outcomes between the avelumab plus axitinib and sunitinib arms within NER subgroups. PFS and OS were estimated using the Kaplan-Meier method; the Cox proportional hazards model was used to compute the HRs and corresponding 95% CIs. ORRs and corresponding 95% CIs were calculated using the Clopper-Pearson method. Multivariable Cox regression analyses to assess the effect of NER after adjustment for other baseline variables were also conducted. NER was evaluated as both a dichotomised and a continuous variable to minimise the potential impact of outlier values and to assess the robustness of the analysis. A stepwise selection procedure was followed to identify explanatory variables of potential prognostic value (initial variables included were age, sex, race, ethnicity, pooled geographical region, ECOG PS, prior nephrectomy, IMDC prognostic criteria and Memorial Sloan Kettering Cancer Center prognostic criteria). Interaction between NER level and treatment arm was assessed in standalone analyses. All analyses reported are exploratory and were performed for hypothesis-generating purposes only.

RESULTS

Patients and baseline NER

The overall study population comprised 886 patients randomised to receive either avelumab plus axitinib (n=442) or sunitinib (n=444), including 560 (63.2%) with PD-L1+ tumours (avelumab plus axitinib arm, n=270; sunitinib arm, n=290).[26] At the data cut-off date (28 April 2020), duration of follow-up was ≥28 months in all patients. NER was evaluable in 383 patients in the avelumab plus axitinib arm and 396 patients in the sunitinib arm. Median (range) NER in the avelumab plus axitinib and sunitinib arms at baseline was 29.2 (3.0 to 3571.0) and 27.0 (2.5 to 1682.0), respectively. Median NER in the overall population at baseline was 28.0 (2.5 to 3571.0). In the avelumab plus axitinib arm, 191 patients had NER <median and 192 had NER ≥median, of whom 118 (61.8%) and 115 (59.9%) had PD-L1+ tumours, respectively. In the sunitinib arm, 195 patients had NER <median and 201 had NER ≥median, of whom 138 (70.8%) and 120 (59.7%) had PD-L1+ tumours, respectively.

Progression-free survival

In patients with NER <median versus NER ≥median in the overall population in the avelumab plus axitinib arm, median PFS (95% CI) was 15.5 (12.0 to 20.6) versus 11.1 (9.5 to 15.1) months, respectively (stratified HR 0.81 (95% CI 0.630 to 1.035); figure 1). In the PD-L1+ population in the avelumab plus axitinib arm, median PFS (95% CI) was 17.8 (12.4 to 23.5) months in patients with NER <median versus 9.8 (8.4 to 13.9) months in patients with NER ≥median (stratified HR 0.72 (95% CI 0.520 to 0.986); figure 2). In patients with NER <median versus NER ≥median in the overall population in the sunitinib arm, median PFS (95% CI) was 9.7 (8.1 to 11.2) versus

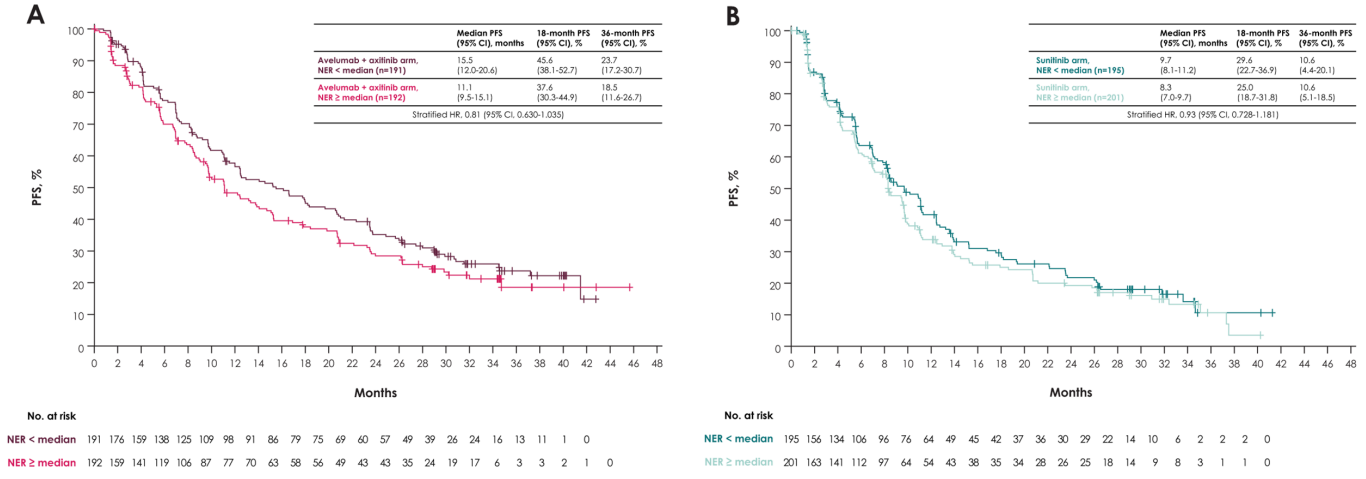

Figure 1 Progression-free survival (PFS) in the overall population according to baseline neutrophil-to-eosinophil ratio (NER) in the (A) avelumab plus axitinib arm and (B) sunitinib arm.

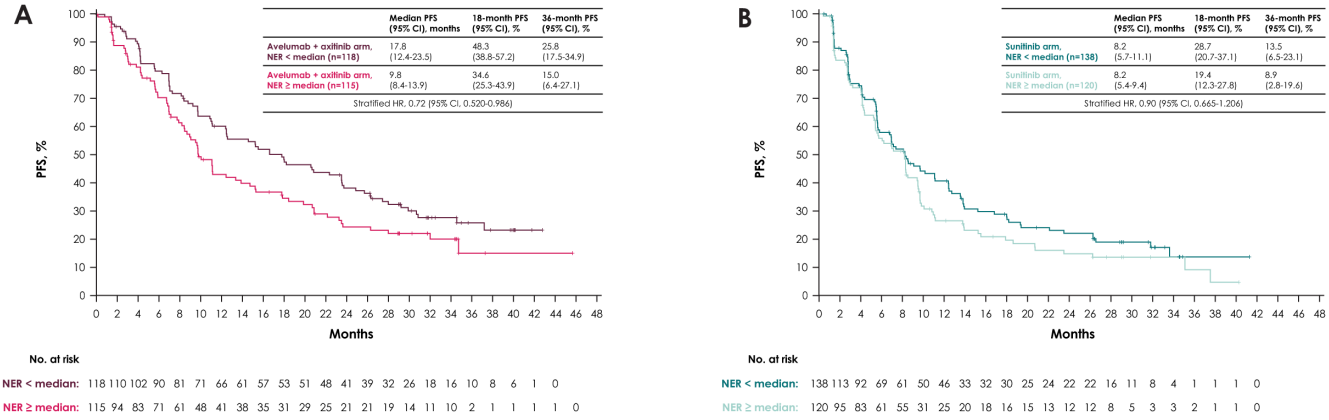

Figure 2 Progression-free survival (PFS) in the programmed death ligand 1 (PD-L1+) population according to baseline neutrophil-to-eosinophil ratio (NER) in the (A) avelumab plus axitinib and (B) sunitinib arm.

8.3 (7.0 to 9.7), respectively (stratified HR 0.93 (95% CI 0.728 to 1.181); figure 1). In the PD-L1+ population in the sunitinib arm, median PFS (95% CI) was 8.2 (5.7 to 11.1) months in patients with NER <median versus 8.2 (5.4 to 9.4) months in patients with NER ≥median, respectively (stratified HR 0.90 (95% CI 0.665 to 1.206); figure 2).

Within NER subgroups, the HR for PFS with avelumab plus axitinib versus sunitinib in patients with NER <median in the overall population was 0.61 (95% CI 0.472 to 0.777; online supplemental figure 1), with a lower HR observed in the PD-L1+ population (HR 0.50 (95% CI 0.358 to 0.687); online supplemental figure 2). Observations were similar in patients with NER ≥median for the overall population (HR 0.74 (95% CI 0.582 to 0.942); online supplemental figure 1) compared with the PD-L1+ population (HR 0.65 (95% CI 0.475 to 0.883); online supplemental figure 2).

In multivariable analyses of PFS, the p value for the association between PFS and NER was p=0.2909 when NER was included as a dichotomised variable (ie, NER <median or ≥median), and p=0.0029 when NER was included as a continuous variable (online supplemental table 1). In interaction tests between treatment and NER for PFS, p values were p=0.7929 for NER as a dichotomised variable and p=0.0387 for NER as a continuous variable.

Overall survival

In the avelumab plus axitinib arm in the overall population, median OS (95% CI) was not reached (not estimable (NE)) in patients with NER <median versus not reached (27.7 months to NE) in patients with NER ≥median (stratified HR 0.67 (95% CI 0.481 to 0.940); figure 3). In the PD-L1+ population in the avelumab plus axitinib arm, median OS (95% CI) was not reached (40.0 months to NE) in patients with NER <median versus 33.0 months (23.3 months to NE) in patients with NER ≥median (stratified HR 0.65 (95% CI 0.422 to 0.988); figure 4). In the sunitinib arm in the overall population, median OS (95% CI) in patients with NER <median versus NER ≥median was not reached (38.0 months to NE) versus 28.1 (22.4 to 35.0) months, respectively (stratified HR 0.57 (95% CI 0.424 to 0.779)) (figure 3). In the PD-L1+ population, within the sunitinib arm in patients with NER <median versus NER ≥median, median OS (95% CI) was not reached (36.2 months to NE) versus 24.8 (21.1 to

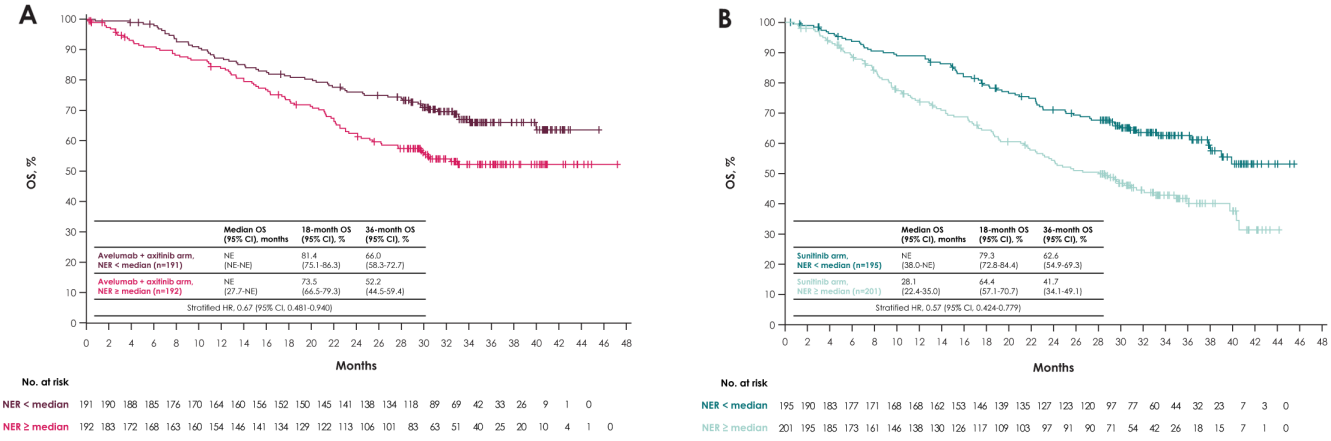

Figure 3 Overall survival (OS) in the overall population according to baseline neutrophil-to-eosinophil ratio (NER) in the (A) avelumab plus axitinib arm and (B) sunitinib arm. NE, not evaluable.

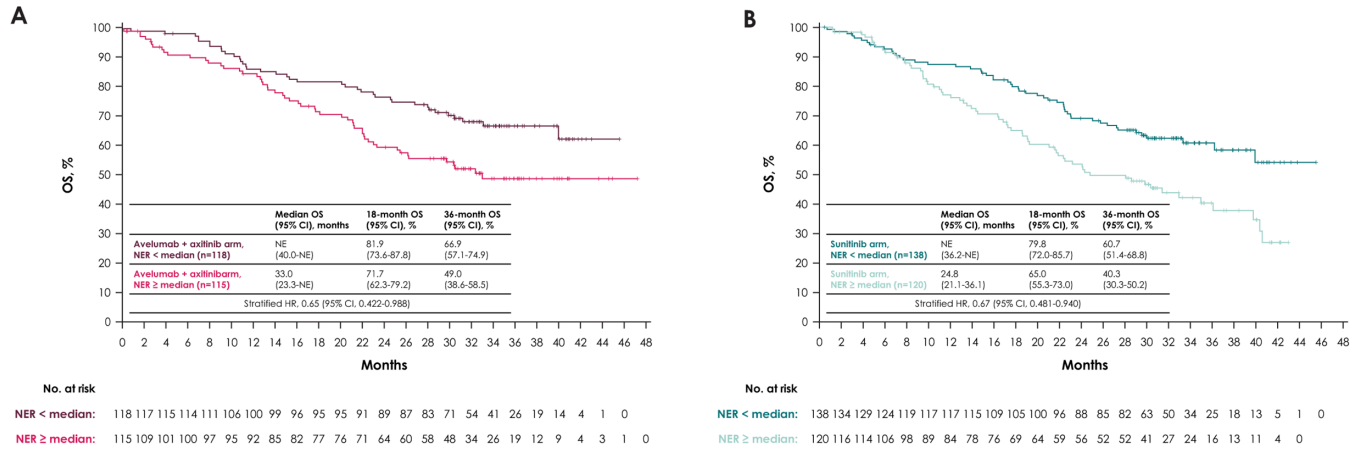

Figure 4 Overall survival (OS) in the programmed death ligand 1 (PD-L1+) population according to baseline neutrophil-to-eosinophil ratio (NER) in the (A) avelumab plus axitinib and (B) sunitinib arm. NE, not evaluable.

36.1), respectively (stratified HR 0.60 (95% CI 0.416 to 0.874); figure 4).

Within NER subgroups in the overall population, the HR for OS with avelumab plus axitinib versus sunitinib in the overall population was 0.79 (95% CI 0.559 to 1.119) in the NER <median subgroup, and 0.71 (95% CI 0.538 to 0.948) in the NER ≥median subgroup (online supplemental figure 3). Within NER subgroups in the PD-L1+ population, the HR for OS was 0.75 (95% CI 0.490 to 1.161) in the NER <median subgroup, and HR 0.73 (95% CI 0.508 to 1.045) in the NER ≥median subgroup (online supplemental figure 4).

In multivariable analyses of OS, the p value for the association between OS and NER was p=0.0896 when NER was included as a dichotomised variable, and p=0.1021 when NER was included as a continuous variable (online supplemental table 2). In interaction tests between treatment and NER for OS, p values were p=0.5673 for NER as a dichotomised variable and p=0.0165 for NER as a continuous variable .

Objective response rates

In the avelumab plus axitinib arm in the overall population, the ORR (95% CI) in patients with NER <median versus NER ≥median was 63.9% (56.6 to 70.7) versus 55.2% (47.9 to 62.4), with complete response (CR) rates of 7.9% versus 2.6%, respectively. In the avelumab plus axitinib arm in the PD-L1+ population, the ORR (95% CI) was 69.5% (60.3 to 77.6) in patients with NER <median versus 59.1% (49.6 to 68.2) in patients with NER ≥median, with CR rates of 10.2% versus 3.5%, respectively (figure 5, online supplemental table 3). In the sunitinib arm in the overall population, the ORR (95% CI) in patients with NER <median versus NER ≥median was 32.8% (26.3 to 39.9) versus 30.8% (24.5 to 37.7), with CR rates of 4.6% versus 2.0%, respectively. In the sunitinib

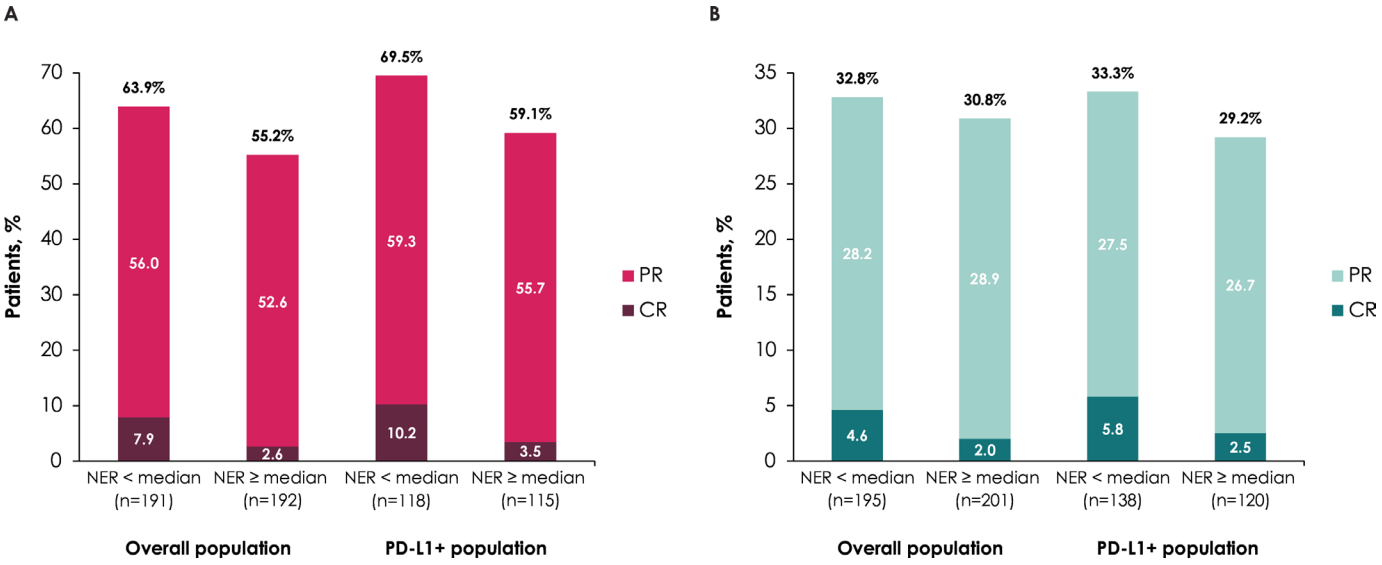

Figure 5 Objective response rates according to baseline neutrophil-to-eosinophil ratio (NER) in the overall and programmed death ligand 1 (PD-L1+) population in the (A) avelumab plus axitinib arm and (B) sunitinib arm. CR, complete response; PR, partial response.

arm in the PD-L1+ population, the ORR was 33.3% (25.5 to 41.9) in patients with NER <median versus 29.2% (21.2 to 38.2) in patients with NER ≥median, with CR rates of 5.8% versus 2.5%, respectively.

NER and tumour gene expression profiling

Tumour gene expression profiling was compared between patients with NER <median versus NER ≥median across both subgroups, including immune gene expression signatures and expression of individual genes (online supplemental figure 5). However, no differences in gene expression signatures were observed between NER subgroups, and no individual gene expression was significantly associated with any NER subgroup.

DISCUSSION

Only a subset of patients with aRCC have a long-term benefit with ICI-based treatment, highlighting a need for predictive and prognostic biomarkers to guide treatment strategies.[33] Although various potential biomarkers have been examined, identification of a biomarker specifically relevant to ICI-based treatment in aRCC is an unmet need. In the post hoc, hypothesis-generating analyses reported here, efficacy outcomes were assessed in patients with aRCC who received 1L treatment with avelumab plus axitinib or sunitinib according to baseline NER.

In both the avelumab plus axitinib and sunitinib arms, a potential increase in OS was observed in patients who had NER <median compared with patients who had NER ≥median at baseline. In analyses of PFS and ORR, greater differences were observed between the NER <median versus NER ≥median subgroups in the avelumab plus axitinib arm than in the sunitinib arm, particularly in patients with PD-L1+ tumours, but analyses were inconclusive overall. In both NER subgroups, efficacy analyses favoured the avelumab plus axitinib arm versus the sunitinib arm, with the greatest differences between arms in PFS and ORR seen in the subgroup of patients who had a PD-L1+ tumour and NER <median. In multivariable analyses, which were performed using a stepwise selection procedure for the regression analysis with a range of baseline variables, including IMDC score, a potential association ($p < 0.05$) between NER and PFS was seen when NER was included as a continuous variable but not as a dichotomised variable (ie, median cut-off), whereas no association was seen between OS and NER. In interaction tests between treatment and NER for PFS and OS, p values were <0.05 for NER as a continuous variable but not as a dichotomised variable. Based on these observations, baseline NER may be prognostic for patients with aRCC regardless of treatment. Results from multivariable analyses and interaction tests suggest that avelumab plus axitinib and sunitinib might have differential effects based on NER level, but that the relationship is complex.

Given the notable associations of previously reported gene expression signatures (GES) with outcomes in IMmotion 150 (angiogenesis GES, myeloid-inflamed GES and T-effector GES) and JAVELIN Renal 101 (angiogenesis GES and immune GES), we evaluated differences in tumour gene expression profiles according to baseline NER.[28 30 31] However, baseline NER level was not associated with any specific GES or individual gene expression.

Findings from analyses of NER differ from previous analyses of NLR as a biomarker in the JAVELIN Renal 101 trial. NLR was found to be a potential prognostic biomarker in patients treated with avelumab plus axitinib or sunitinib but was not predictive of differential outcomes in either arm.[17] In addition, NLR was associated with biological characteristics that may influence patient outcomes on their own, such as tumour mutational burden, mutational signatures and IMDC risk groups. In previous studies, eosinophils have been shown to be active in the tumour microenvironment and to be involved in response to immunotherapies in preclinical models.[24 34] Specifically, activated tumour-infiltrating eosinophils were found to release chemokines that promoted T-cell recruitment and infiltration into the tumour and macrophage polarisation, resulting in tumour rejection and prolonged survival.

In a previous study of nivolumab plus ipilimumab treatment in patients with metastatic RCC, lower baseline NER was associated with longer PFS and OS and higher ORR.[20 35] However, to our knowledge, our study is the first to evaluate baseline NER in patients receiving anti-angiogenic TKI monotherapy and to compare outcomes with those in patients receiving ICI-based combination therapy. Our analyses have various limitations and the findings should be interpreted with caution. All analyses were exploratory and were performed for hypothesis-generating purposes only. Median cutoffs were used to provide an estimation of possible trends only. Multivariable analyses included only a selected set of variables and did not include other potential blood-based or inflammatory biomarkers, such as levels of individual cell types. More comprehensive evaluation of NER as a potential predictive biomarker in patients with aRCC receiving ICI-based combinations is needed.

CONCLUSION

Post hoc analysis from the JAVELIN Renal 101 trial suggests that lower baseline NER may be associated with longer OS irrespective of treatment. Analyses of potential differences in treatment effects with avelumab plus axitinib versus sunitinib according to NER level were inconclusive.

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Acknowledgements The authors would like to thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centres and at Pfizer.

Contributors Conceptualisation: MT and Y-WC. Data analysis: BH and RA. Data collection: MT, MHV, BAM, MAB, M-OG, PN, CK, YT and BIR. Trial oversight: BH, MM and AdP. All authors had full access to all data in the study and contributed to data interpretation, manuscript writing and review. All authors approved the submission of the manuscript. Guarantor, MT.

Funding This trial was sponsored by Pfizer and was previously conducted under an alliance between Merck (CrossRef Funder ID: 10.13039/100009945) and Pfizer. Medical writing support was provided by Hiba Al-Ashtal of Nucleus Global and was funded by Merck and Pfizer. MHV is supported (in part) by an NIH/NCI Cancer Center Support Grant/Core Grant (P30 CA008748).

Competing interests MHV owns stock and other ownership interests in CellGenix; has received honoraria from Bristol Myers Squibb; reports providing a consulting or advisory role for AVEO, Calithera Biosciences, Corvus Pharmaceuticals, Eisai, Exelixis, MSD, and Pfizer; has received research funding from Pfizer; has received reimbursement for travel and accommodations expenses from AstraZeneca/MedImmune; and has another relationship with Bristol Myers Squibb. BAM reports grants and personal fees from Pfizer during the conduct of the study as well as personal fees from Astellas and Seagen; grants and personal fees from Bristol Myers Squibb and Exelixis; personal fees from Eisai; grants and personal fees from Calithera; and personal fees from Dendreon, Merck, and MSD, outside the submitted work. MAB reports providing a consulting or advisory role for Exelixis, Bayer, Bristol Myers Squibb, Eisai, Pfizer, AstraZeneca, Janssen, Calithera Biosciences, Genomic Health, Nektar, and Sanofi; and has received research funding from Xencor, Bayer, Bristol Myers Squibb, Genentech/Roche, Seagen, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peloton Therapeutics, and Pfizer outside the submitted work. M-OG reports providing a consulting or advisory role for AstraZeneca, Bristol Myers Squibb, Ipsen, MSD, ONO, Pfizer, Astellas Pharma, and EUSA; has received reimbursement for travel and accommodations expenses from Bristol Myers Squibb, Merck; has received honoraria from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Medac, MSD, Novartis, ONO, Pfizer, Ipsen, Merck, and EUSA; and has received research funding from Bristol Myers Squibb (Inst), and Intuitive Surgical (Inst). PN reports providing a consulting or advisory role for AstraZeneca, Bristol Myers Squibb, Immunocore, MSD, Pfizer, Pierre Fabre, Novartis, GSK, Ipsen, 4SC, and Merck; has provided speaker services for Bristol Myers Squibb, Merck, MSD, and Novartis; and has received reimbursement for travel and accommodations expenses from Bristol Myers Squibb and MSD. CK reports providing a consulting or advisory role for Pfizer, Novartis, Bristol Myers Squibb, Astellas Pharma, Ipsen, Eisai, and Janssen; has received reimbursement for travel and accommodations expenses from Pfizer, Novartis, and Eisai; and has received honoraria from Pfizer, Novartis, Bristol Myers Squibb, Ipsen, Merck, and MSD. YT reports providing a consulting or advisory role for Eisai, MSD, Ono Pharmaceutical; has received honoraria from Astellas Pharma, Bristol Myers Squibb Japan, Chugai Pharma, Novartis, Ono Pharmaceutical; and has received research funding from Astellas Pharma, AstraZeneca, Chugai Pharma, Eisai, MSD, Novartis, Ono Pharmaceutical, Pfizer, Takeda. BH is an employee of Pfizer and reports stock and other ownership interests with Pfizer. RA is an employee of Pfizer. MM is an employee of Pfizer and owns stock and other ownership interests in Pfizer. AdP is an employee of Pfizer and owns stock and other ownership interests in Pfizer; and has received honoraria from Pfizer. BR reports providing a consulting or advisory role for 3D Medicines, Aravive, Arrowhead Pharmaceuticals, Aveo, Bristol Myers Squibb, Corvus Pharmaceuticals, Eisai, GlaxoSmithKline, Pfizer, Merck, Shionogi, Surface Oncology, and Synthorx; reports leadership with MJH Life Sciences; has received travel, accommodations, and expenses from Bristol Myers Squibb, Merck, and Pfizer; reports stock and other ownership interests from PTC Therapeutics; and has received research funding from Aravive, Arrowhead Pharmaceuticals, AstraZeneca/MedImmune, Bristol Myers Squibb, Dragonfly Therapeutics, Immunomedics, Incyte, Exelixis, Merck, Pfizer, Roche/Genentech, Seattle Genetics, Surface Oncology, and Taris.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The trial was conducted in accordance with the ethics principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. The protocol, amendments, and informed consent forms were approved by an institutional review board or independent ethics committee at each study site. The approval number from the Vanderbilt University Medical Center Institutional Review Board for the work reported (Drs Tucker, Chen, and Rini) was 160979. A list of the study sites has been provided as a separate file. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. 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 deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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