Association of Neutrophil-to-Lymphocyte Ratio with Efficacy of First-Line Avelumab plus Axitinib vs. Sunitinib in Patients with Advanced Renal Cell Carcinoma Enrolled in the Phase 3 JAVELIN Renal 101 Trial

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ABSTRACT

Purpose: To evaluate the association between neutrophil-to-lymphocyte ratio (NLR) and efficacy of avelumab plus axitinib or sunitinib.

Experimental Design: Adult patients with untreated advanced renal cell carcinoma (RCC) with a clear-cell component, ≥1 measurable lesions, Eastern Cooperative Oncology Group performance status of 0 or 1, fresh or archival tumor specimen, and adequate renal, cardiac, and hepatic function were included. Retrospective analyses of the association between baseline NLR and progression-free survival (PFS) and overall survival (OS) in the avelumab plus axitinib or sunitinib arms were performed using the first interim analysis of the phase 3 JAVELIN Renal 101 trial (NCT02684006). Multivariate Cox regression analyses of PFS and OS were conducted. Translational data were assessed to elucidate the underlying biology associated with differences in NLR.

Results: Patients with below-median NLR had longer observed PFS with avelumab plus axitinib [stratified HR, 0.85; 95% confidence interval (CI), 0.634–1.153] or sunitinib (HR, 0.56; 95% CI, 0.415–0.745). In the avelumab plus axitinib or sunitinib arms, respectively, median PFS was 13.8 and 11.2 months in patients with below-median NLR, and 13.3 and 5.6 months in patients with median-or-higher NLR. Below-median NLR was also associated with longer observed OS in the avelumab plus axitinib (HR, 0.51; 95% CI, 0.300–0.871) and sunitinib arms (HR, 0.30; 95% CI, 0.174–0.511). Tumor analyses showed an association between NLR and key biological characteristics, suggesting a role of NLR in underlying mechanisms influencing clinical outcome.

Conclusions: Current data support NLR as a prognostic biomarker in patients with advanced RCC receiving avelumab plus axitinib or sunitinib.

Introduction

Renal cell carcinoma (RCC) accounts for 2% to 3% of all adult malignancies, with an annual incidence of 338,000 new cases and 144,000 deaths globally (1, 2). In recent years, the number of treatment options for advanced RCC has expanded, owing to the development of novel therapies such as immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors (TKI; ref. 3). However, a need remains for reliable pretreatment predictive markers that can improve the prognosis of RCC and guide treatment decisions (4).

Immune response and systemic inflammation are being increasingly recognized as a crucial component in cancer development and progression. In particular, neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential biomarker, providing a new perspective for predicting the prognosis of cancer in a variety of solid tumors (4–8). Preliminary data from studies that evaluated the prognostic value of NLR indicate that this systemic inflammatory biomarker could be a reliable, universally available, and inexpensive prognostic marker in advanced RCC. In these studies, low baseline NLR was significantly associated with superior progression-free survival (PFS; refs. 3, 6, 9–11) and overall survival (OS; refs. 3, 6, 9, 10, 12) in patients with advanced RCC. Two additional studies showed that NLR variations during treatment (measured at 6 weeks) were similarly associated with these clinical outcomes (9, 13). In the studies that suggested a prognostic association between NLR and PFS or OS, patients received monotherapy, including with ICIs (3, 9, 11) and TKIs (10–12). A recent meta-analysis reported the role of NLR in RCC; however, this study lacked sensitivity and a subgroup analysis to account for potential sources of heterogeneity (14). Nevertheless, an overall review of the literature indicates a lack of data from robust studies investigating NLR as a potential prognostic biomarker in patients with advanced RCC treated with recently approved ICI plus TKI combination treatments.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Biomarkers are needed to improve outcomes from therapies, including immunotherapies such as anti–programmed death 1 or anti–programmed death ligand 1 monoclonal antibodies, for patients with advanced renal cell carcinoma (RCC). Data from the randomized phase 3 JAVELIN Renal 101 trial showed that patients with below-median neutrophil-to-lymphocyte ratio (NLR) had longer observed progression-free survival with avelumab plus axitinib [stratified HR, 0.85; 95% confidence interval (CI), 0.634–1.153] or sunitinib (stratified HR, 0.56; 95% CI, 0.415–0.745) than those with median-or-higher NLR. Deeper analysis of the tumors in this study also revealed an association between NLR and key biological characteristics associated with the tumor microenvironment. Importantly, and of clinical relevance, is that median baseline NLR may be useful as a prognostic biomarker in patients with advanced RCC.

We conducted this analysis to evaluate the association of baseline NLR with efficacy outcomes in patients with advanced RCC receiving ICI plus TKI combination therapy (avelumab plus axitinib) and thereby assess its potential as a biomarker. For this purpose, we used data from the randomized, phase 3 JAVELIN Renal 101 trial (15, 16), which investigated the efficacy and safety of the combination of avelumab, a human monoclonal programmed death ligand 1 (PD-L1) antibody (17), plus axitinib, a selective TKI of VEGF receptor 1, 2, and 3 (18), compared with sunitinib, a multitargeted TKI (19), in previously untreated patients with advanced RCC. At the time of the first interim analysis, avelumab plus axitinib demonstrated a significant improvement in PFS compared with sunitinib [HR, 0.69; 95% confidence interval (CI), 0.56–0.84; $P < 0.001$], but OS data were immature at the time of data cutoff (HR, 0.78; 95% CI, 0.55–1.08; $P = 0.14$; ref. 15). The objective response rate (ORR) with combination therapy was twice that with sunitinib (51.4%; 95% CI, 46.6–56.1 vs. 25.7%; 95% CI, 21.7–30.0; ref. 15).

Here, we investigate the correlation of baseline NLR with clinical outcomes in patients with advanced RCC receiving ICI plus TKI combination therapy. Importantly, we expand on the JAVELIN Renal 101 data by analyzing a range of translational data to elucidate the underlying biology associated with differences in NLR.

Materials and Methods

Study design and participants

The patient eligibility criteria and trial design for JAVELIN Renal 101 (ClinicalTrials.gov, NCT02684006) trial have been described previously (15). Briefly, JAVELIN Renal 101 is a multicenter, randomized, open-label, phase 3 trial that was conducted to compare the efficacy and safety of avelumab plus axitinib with the previous standard-of-care sunitinib in treatment-naive patients with advanced RCC with a clear-cell component. All patients were required to be at least 18 years of age, with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors version 1.1; an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 (based on a scale from 0 to 5, with higher numbers indicating greater disability); a fresh or archival tumor specimen; and adequate renal, cardiac, and hepatic function. Patients who had an absolute neutrophil count $<1.5 \times 10^9$/L or any persisting toxicity of grade >1 (National Cancer Institute Common Terminology Criteria for Adverse Events v4.0) were excluded. Patients who had active nervous system metastases or autoimmune disease or who had taken an immunosuppressant within 7 days before randomization were also excluded.

Enrolled patients were randomized 1:1 to receive avelumab plus axitinib ($n = 442$) or sunitinib ($n = 444$). The stratification factors were based on ECOG PS score (0 vs. 1) and geographical region (United States vs. Canada or Western Europe vs. the rest of the world). Avelumab 10 mg/kg was administered as a 1-hour intravenous infusion every 2 weeks, axitinib 5 mg was administered orally twice daily in a 6-week cycle, and sunitinib 50 mg was administered orally once daily (4 weeks on, 2 weeks off). The study protocol, amendments, and informed consent forms were approved by the institutional review board or independent ethics committee at each trial site.

The trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written, informed consent before enrolment. The protocol was approved by the institutional review board or independent ethics committee at each participating center.

Study assessments

The primary endpoint of JAVELIN Renal 101 was to demonstrate superiority of avelumab plus axitinib over sunitinib in terms of PFS by blinded independent central review (BICR) and OS in patients with PD-L1–positive tumors (PD-L1 expression on ≥1% of immune cells). PFS by BICR and OS in all patients were assessed as key secondary endpoints. Our study investigated associations of NLR with antitumor endpoints in all patients (irrespective of PD-L1 status). Additional endpoints included objective response by BICR and translational biomarker analysis.

NLR was calculated as the absolute count of neutrophils (per nL) divided by the absolute count of lymphocytes (per nL). NLR values were gathered from the last blood test within 28 days before the first infusion of study treatment. Patients with nonmissing neutrophil and lymphocyte counts at baseline were included in the analysis set.

Translational biomarker analyses

All analyses were performed on archival tumor samples or samples collected during a new biopsy procedure from primary or metastatic sites. Various translational biomarker analyses were performed using identical methodologies to those reported in a previous study (20).

Immunohistochemical analysis

PD-L1 expression on tumor cells and immune cells was assessed at a central laboratory using the Ventana PD-L1 (SP263) assay (Ventana Medical Systems; 740–4907). The threshold of ≥1% of tumor-infiltrating immune cells staining positive within the tumor area of the tested tissue sample defined the official PD-L1 status of a given sample, but tumor cell expression was also evaluated as an exploratory variable. CD8 expression was assessed by immunohistochemistry using clone C8/144B (M710301–2) and scored via a quantitative method using image analysis software (Definiens; ref. 20). A central tumor region was delineated by a pathologist. At the interface between malignant and adjacent normal tissue, a 1,000-μm–wide immune margin (IM), an immunologically active region and site of PD-L1 expression (21), centered around the perimeter was generated. For both the central tumor region and the IM, the relative area of marker-positive cells (i.e., the $CD8^+$ area relative to the total tumor area) was calculated. CD8 expression was reported in terms of the percentage of $CD8^+$ cells in relation to the total number of $CD8^+$ cells in the total

tumor area, tumor center, or IM, with the median as the cutoff point value (20).

Whole-exome sequencing, variant calling, copy-number variations, and tumor mutational burden

Whole-exome sequencing (WES) data were generated for 733 patients ($n = 358$, avelumab plus axitinib arm; $n = 375$, sunitinib arm) from formalin-fixed paraffin-embedded (FFPE) tumor tissue [Accuracy and Content Enhanced (ACE) version 3; Illumina NovaSeq] and processed by the Personalis ACE Cancer Exome pipeline, which uses BWA, GATK, MuTect, Vardict, and Picard to generate variant calls (20). Variant calls were further filtered by the vendor using Personalis proxy-normal and custom filters to remove many germline variants found in normal tissue. Mutations with a minimum of 5 mutant reads (i.e., found on at least 5 separate DNA molecules in an individual tumor sample) that were not annotated as synonymous variants and annotated as resulting in a change in protein coding sequence were included in the analysis. Copy-number variations (CNV) were called using FACETS on the tumor samples (22). Chromosome instability was computed as weighted-genomic integrity index score from CNVs calculated as described previously. WES data were used to calculate the global median tumor mutational burden (TMB) defined as number of non-synonymous mutations per megabase; patients were then divided on the basis of the global median value into below-median TMB and median-or-higher TMB.

RNA sequencing, transcript quantification, pathway and deconvolution analyses

Whole-transcriptome profiles were generated for 720 patients ($n = 350$, avelumab plus axitinib arm; $n = 370$, sunitinib arm) using RNA sequencing (RNA-seq; ACE version 3; Illumina NovaSeq) on FFPE tumor tissue (20). Transcript levels were quantified using the Personalis ACE Cancer Transcriptome Analysis pipeline, which uses STAR version 2.4.2a-p1 to align reads to the National Center for Biotechnology Information hs37d5 annotation 105 reference genome and produces transcripts per million (TPM) values for each gene. TPM values were $\log_2$ transformed for further analysis of individual genes or standardized gene pathway signature scores. Briefly, for each gene we calculated the mean expression and SD across samples. Then, we subtracted the mean and divided by the SD to standardize the gene score to be centered at zero with units of SD (Z score; ref. 20).

Gene signature scores were computed from the average expression of genes within a pathway or module. A univariate Cox proportional hazards model was used to assess the association of PFS with each signature, and then groups were categorized into high- and low-median NLR signature scores (23, 24). Multivariate analysis adjusting for age and sex was also performed. Modules were annotated through identifying top-enriched gene sets via hypergeometric tests using public gene set collections, including the MsigDB Hallmark, GO Biological Process, and LM22 (25–27). RNA-seq data were deconvoluted into LM22 IC proportions by ImmuneNet (Data4Cure; Supplementary Table S1; ref. 28), an implementation of the support vector regression method described previously by Newman and colleagues (25).

The various biomarker-derived classifications from prespecified analyses of secondary endpoints and *post hoc* exploratory analyses noted previously were then used to link these results to the NLR status defined by dichotomization based on median NLR (below-median NLR or median-or-higher NLR). Subsequently, Kaplan–Meier analysis was performed to evaluate the association between PFS and the variables. Cox proportional hazards models were used to calculate HR and 95% CI; P values were determined by 1- or 2-sided log-rank test as indicated. The logistic regression analyses were performed using Data4Cure MDCA (multinomial discrete choice analysis) tools with median-or-higher NLR defined as the reference group. A positive logistic regression coefficient indicated a higher gene expression signature in the below-median NLR group, and a negative logistic regression coefficient indicated a higher gene expression signature in the median-or-higher NLR group. Data were plotted using the nominal P values. False discovery rates and resultant q values were computed from the P values following adjustment for multiple hypothesis testing in the Data4Cure analyses; however, because none of the q values were <0.05 (an expected result for datasets of this size), the specific calculations have not been reported.

Statistical analyses

We evaluated the association between NLR and efficacy outcomes in patients with RCC using data from the first interim analysis (data cutoff, June 20, 2018) of JAVELIN Renal 101. This included 873 evaluable patients: 434 in the avelumab plus axitinib arm and 439 in the sunitinib arm (15). Patients in each treatment arm were dichotomized on the basis of median NLR (below-median NLR or median-or-higher NLR). The median was determined for all randomized patients. To analyze the combined effect of NLR and TMB on efficacy, patients with below-median or median-or-higher NLR values were further divided into subgroups with below-median or median-or-higher TMB. PFS per BICR and OS for all treatment arms were summarized using the Kaplan–Meier method. The Cox proportional hazards model was fitted to compute the HR and the corresponding 95% CI. Multivariate Cox regression analyses of PFS and OS were also performed, treating NLR as a continuous variable after adjusting baseline covariates [covariates included sex, age, International Metastatic RCC Database Consortium (IMDC) Risk Score, prior nephrectomy, Memorial Sloan Kettering Cancer Center risk score, and geographic region]. We also evaluated the predictive effect of NLR by testing the interaction of the treatment group with NLR in the multivariate Cox regression model. The proportion of patients with confirmed objective response was calculated with corresponding 95% CI using the Clopper–Pearson method. The details of the translational biomarker analysis are provided in the Supplementary Data.

Results

NLR

NLR was evaluable in 434 patients in the avelumab plus axitinib arm and 439 patients in the sunitinib arm. The median NLR was 2.8 (range, 0.5–24.3) in the avelumab plus axitinib arm and 2.8 (range, 0.4–41.0) in the sunitinib arm. The median NLR in the overall population was 2.8 (range, 0.4–41.0).

PFS

In both treatment arms, the observed PFS was longer in patients with below-median NLR than in those with median-or-higher NLR, with a stratified HR of 0.85 (95% CI, 0.634–1.153) in the avelumab plus axitinib arm (**Fig. 1A**) and 0.56 (95% CI, 0.415–0.745) in the sunitinib arm (**Fig. 1B**). Median PFS was 13.8 months (95% CI, 11.1 months to not estimable, NE) in patients with below-median NLR and 13.3 months (95% CI, 8.4 months to NE) in patients with median-or-higher NLR in the avelumab plus axitinib arm, and the median PFS was 11.2 months (95% CI, 8.4–18.6 months) in patients with below-median NLR and 5.6 months (95% CI, 4.3–7.2 months) in patients

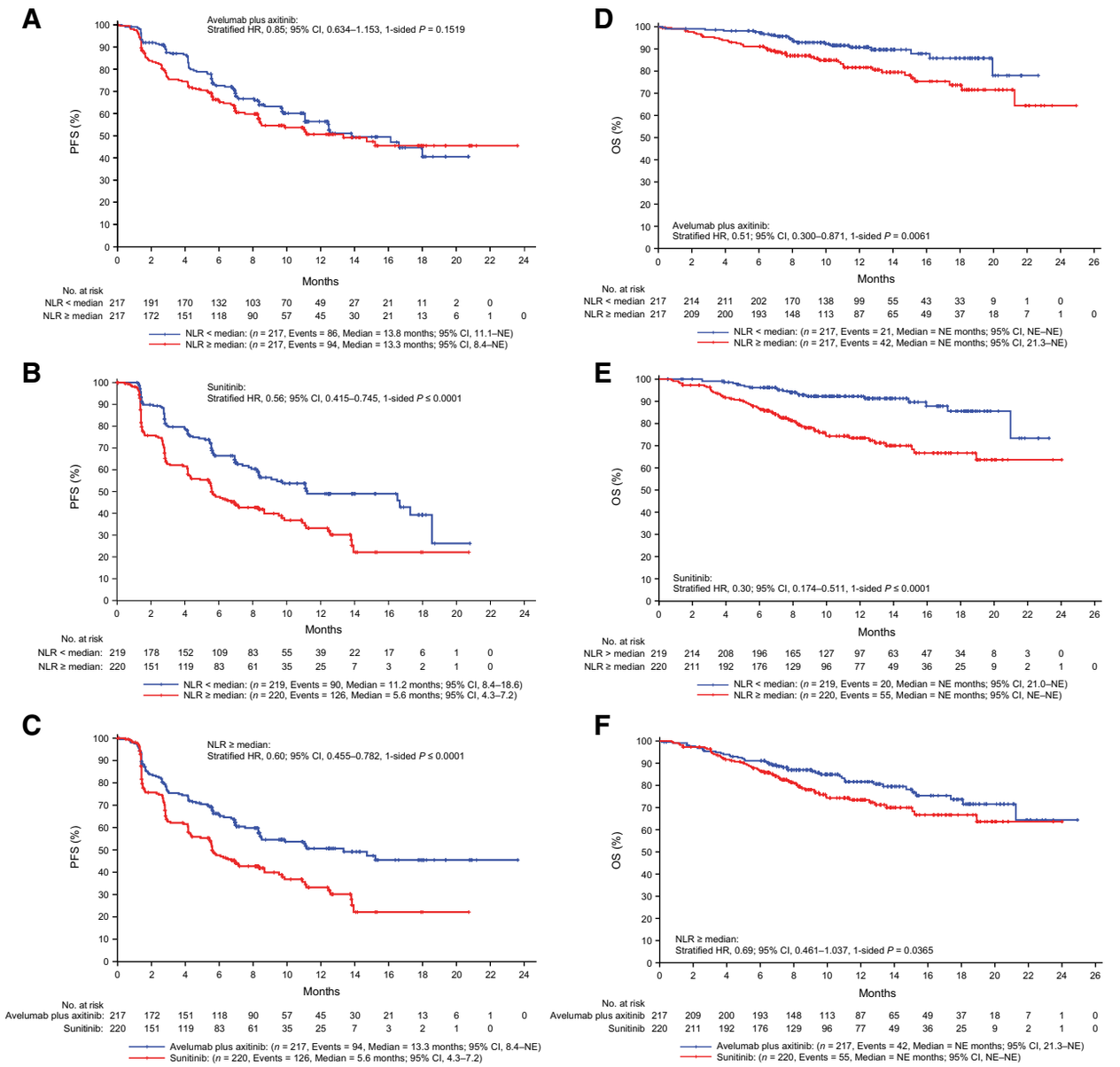

Figure 1.

PFS per BICR according to NLR in the avelumab plus axitinib arm (**A**) and sunitinib arm (**B**) and in patients with a median-or-higher NLR (**C**). OS according to NLR in the avelumab plus axitinib arm (**D**) and sunitinib arm (**E**) and in patients with a median-or-higher NLR (**F**).

with median-or-higher NLR in the sunitinib arm. Event-free probability at 12 months was 56.4% (95% CI, 48.3%-63.7%) in patients with below-median NLR and 50.6% (95% CI, 42.6%–58.1%) in patients with median-or-higher NLR in the avelumab plus axitinib arm, and it was 49.0% (95% CI, 40.4%–57.0%) in patients with below-median NLR and 33.2% (95% CI, 25.6%–41.1%) in patients with median-or-higher NLR in the sunitinib arm. The stratified HR for PFS in patients with median-or-higher NLR in the avelumab plus axitinib arm versus the sunitinib arm was 0.60 (95% CI, 0.455–0.782; **Fig. 1C**).

A multivariate analysis of PFS incorporating various potential prognostic factors showed the prognostic value of NLR as a continuous variable, with a stronger effect observed in the sunitinib arm versus the avelumab plus axitinib arm (**Table 1**). In addition, multivariate analyses treating NLR as a binary variable dichotomized by the median (Supplementary Table S2) showed that below-median NLR was associated with longer PFS. Using the baseline NLR level as a covariate, an interaction test with treatment showed no substantial interaction between treatment group and NLR on PFS ($P = 0.2846$; Supplementary Table S3).

OS

In both treatment arms, the observed OS was longer in patients with below-median NLR than in those with median-or-higher NLR,

Table 1. Multivariate Cox regression analysis of PFS per BICR, treating NLR as a continuous variable.

Variable[a]	Levels	Parameter estimate	Standard error	Wald χ^2 statistic	2-sided *P* value	HR (95% CI)
Avelumab plus axitinib (*n* = 434)						
Baseline NLR		0.06	0.03	5.65	0.0175	
Sex	Male					
	Female	0.28	0.16	3.05	0.0805	1.327 (0.966–1.824)
Age	<65 years					
	≥65 years	−0.33	0.16	4.14	0.0418	0.720 (0.525–0.988)
IMDC risk group	Favorable					
	Intermediate	0.64	0.22	8.21	0.0042	1.897 (1.224–2.939)
	Poor	1.10	0.27	16.44	<0.0001	3.004 (1.765–5.113)
Sunitinib (*n* = 439)						
Baseline NLR		0.06	0.01	19.69	<0.0001	
Geographic region	United States					
	Canada and Western Europe	0.03	0.31	0.01	0.9117	1.035 (0.563–1.905)
	Rest of the world	−0.36	0.37	0.96	0.3282	0.697 (0.339–1.436)
Age	<65 years					
	≥65 years	−0.30	0.15	4.19	0.0407	0.738 (0.551–0.987)
Pooled geographic region	Europe					
	North America	−0.55	0.30	3.27	0.0704	0.579 (0.321–1.047)
	Asia	0.33	0.24	1.82	0.1776	1.387 (0.862–2.230)
	Rest of the world	0.27	0.28	0.93	0.3345	1.307 (0.759–2.249)
Prior nephrectomy	Yes					
	No	−0.49	0.20	6.11	0.0135	0.613 (0.416–0.904)
MSKCC risk group	Favorable					
	Intermediate	0.50	0.19	6.83	0.0090	1.653 (1.134–2.409)
	Poor	1.56	0.27	33.83	<0.0001	4.766 (2.816–8.066)

Abbreviation: MSKCC, Memorial Sloan Kettering Cancer Center.
[a]Explanatory variables were selected using a stepwise selection procedure. The level of significance for an explanatory variable to enter the model was set to 0.15, and the significance level for removing it was set to 0.40; subgroups with <5% of the patient population were pooled.

with a stratified HR of 0.51 (95% CI, 0.300–0.871) in the avelumab plus axitinib arm (**Fig. 1D**) and 0.30 (95% CI, 0.174–0.511) in the sunitinib arm (**Fig. 1E**). However, because OS data were immature at the time of the first interim analysis, median OS had not yet been reached in either arm, irrespective of NLR stratification. The stratified HR for OS in patients with median-or-higher NLR in the avelumab plus axitinib arm versus the sunitinib arm was 0.69 (95% CI, 0.461–1.037; **Fig. 1F**).

As with PFS, a multivariate analysis of OS showed the prognostic value of NLR as a continuous variable, with a stronger effect observed in the sunitinib arm versus the avelumab plus axitinib arm (**Table 2**). Using the baseline NLR level as a covariate, an interaction test with treatment showed no substantial interaction between treatment group and NLR on OS ($P = 0.7700$; Supplementary Table S3).

Response

The ORR was higher in patients with below-median NLR than in those with median-or-higher NLR in both treatment arms (**Fig. 2**). In the avelumab plus axitinib arm, the ORR was 57.1% (95% CI, 50.3%–63.8%) in the below-median NLR group versus 47.5% (95% CI, 40.7%–54.3%) in the median-or-higher NLR group; the complete response rate was 5.5% vs. 1.4%, respectively. In the sunitinib arm, the ORR was 29.7% (95% CI, 23.7%–36.2%) in the below-median NLR group versus 22.3% (95% CI, 17.0%–28.4%) in the median-or-higher NLR group; the complete response rate was 3.7% versus 0%, respectively. The percentage of patients with best overall response of progressive disease in either study arm was nearly doubled in the median-or-higher NLR group compared with the below-median NLR group (15.7% vs. 7.8% in the avelumab plus axitinib arm and 25.5% vs. 12.3% in the sunitinib arm, respectively).

NLR and TMB

In both treatment arms, patients in NLR groups were further divided into below-median TMB and median-or-higher TMB subgroups. In patients in the avelumab plus axitinib arm with median-or-higher NLR, no differences in PFS or OS were observed between subgroups with below-median TMB and median-or-higher TMB. However, in the group with below-median NLR, numerically longer PFS and OS were observed in patients with below-median TMB versus median-or-higher TMB; the HR for PFS was 0.63 (95% CI, 0.369–1.063; $P = 0.0406$) and the HR for OS was 0.35 (95% CI, 0.112–1.122; $P = 0.0333$; **Table 3**). Conversely, in groups of patients in the sunitinib arm with below-median or median-or-higher NLR, no differences in PFS or OS were observed between patients with below-median TMB or median-or-higher TMB. No associations between ORR and combined NLR/TMB subgroups were seen in either treatment arm.

NLR and translational oncology

A range of translational data (including demographics, immunohistochemical, RNA-seq, and WES) were examined, as described previously in the Supplementary Data, to determine the biology underlying differences in NLR. Examination of the demographic data of enrolled patients indicated a high frequency of patients with median-or-higher NLR in the IMDC poor-risk group, which was enriched in the poor-risk group relative to the distribution of patients

Table 2. Multivariate Cox regression analysis of OS per BICR, treating NLR as a continuous variable.

Variable[a]	Levels	Parameter estimate	Standard error	Wald χ^2 statistic	2-sided *P* value	HR (95% CI)
Avelumab plus axitinib (*n* = 434)						
Baseline NLR		0.09	0.04	5.75	0.0164	
Race	Caucasian/White					
	Asian	−0.98	0.42	5.52	0.0188	0.375 (0.165–0.850)
	Other	0.73	0.44	2.77	0.0961	2.078 (0.878–4.918)
Prior nephrectomy	Yes					
	No	0.85	0.29	8.88	0.0029	2.348 (1.339–4.117)
IMDC risk group	Favorable					
	Intermediate	0.79	0.49	2.64	0.1039	2.209 (0.850–5.744)
	Poor	1.57	0.53	8.74	0.0031	4.830 (1.700–13.722)
Sunitinib (*n* = 439)						
Baseline NLR		0.11	0.02	50.08	<0.0001	
Pooled geographic region	Europe					
	North America	−0.48	0.31	2.47	0.1159	0.618 (0.339–1.126)
	Asia	0.09	0.38	0.05	0.8184	1.091 (0.520–2.288)
	Rest of the world	0.88	0.37	5.70	0.0169	2.418 (1.172–4.990)
MSKCC risk group	Favorable					
	Intermediate	1.37	0.52	6.84	0.0089	3.948 (1.411–11.045)
	Poor	2.89	0.56	27.00	<0.0001	18.057 (6.062–53.785)

Abbreviation: MSKCC, Memorial Sloan Kettering Cancer Center.

[a]Explanatory variables were selected using a stepwise selection procedure. The level of significance for an explanatory variable to enter the model was set to 0.15, and the significance level for removing it was set to 0.40; subgroups with <5% of the patient population were pooled (race: Black/African American and Other) or not presented (ethnicity: there were only 2 subgroups, and Hispanic/Latino was <5% of the patient population).

within other categories (Pearson χ^2 test value, 71.47; $P < 0.0001$; Supplementary Fig. S1). Deconvolution analyses revealed an association between median NLR and expression of cell type–specific signatures for M0 and M2 macrophages and resting CD4 memory T cells (Supplementary Fig. S2). Logistic regression analyses of gene expression data, carried out on archival tumor samples (20), revealed differences between tumors with median-or-higher NLR and those with below-median NLR, such as elevated expression of Hallmark

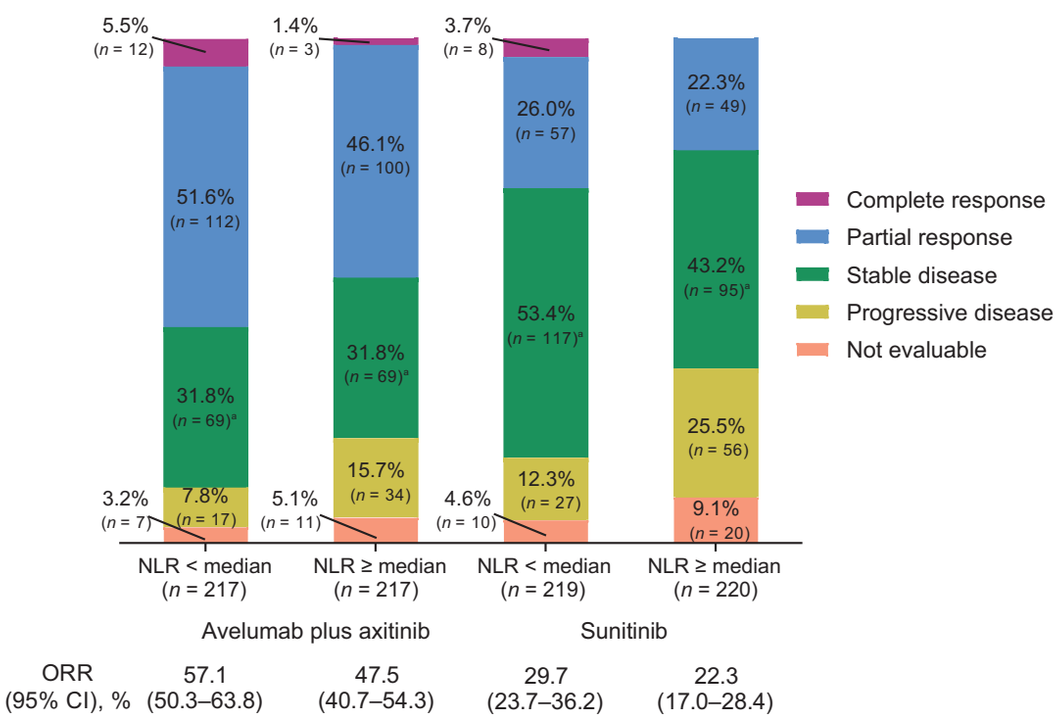

Figure 2.

Response to avelumab plus axitinib or sunitinib dichotomized by NLR. [a]Includes patients with non-complete response/non-progressive disease (*n* = 4; 1.8%).

Table 3. Summary of PFS per BICR, OS, and ORR per BICR by treatment and baseline NLR combined with TMB.

	Below-median NLR		Median-or-higher NLR	
Avelumab plus axitinib	**Below-median TMB ($n = 81$)**	**Median-or-higher TMB ($n = 99$)**	**Below-median TMB ($n = 101$)**	**Median-or-higher TMB ($n = 80$)**
Median PFS (95% CI),[a] months	NE (12.5–NE)	12.6 (8.4–NE)	11.2 (6.9-NE)	NE (7.0–NE)
Stratified HR (95% CI)[b]	0.63 (0.369–1.063)		1.22 (0.733–2.031)	
1-sided *P* value	0.0406		0.7779	
Median OS (95% CI),[a] months	NE (NE–NE)	NE (NE–NE)	NE (NE–NE)	NE (21.3–NE)
Stratified HR (95% CI)[b]	0.35 (0.112–1.122)		1.83 (0.851–3.941)	
1-sided *P* value	0.0333		0.9409	
ORR, *n* (%)	52 (64.2)	54 (54.5)	49 (48.5)	39 (48.8)
95% CI	52.8–74.6	44.2–64.6	38.4–58.7	37.4–60.2
Unstratified odds ratio (95% CI)[c]	1.494 (0.784–2.859)		0.991 (0.528–1.858)	
Sunitinib	**Below-median TMB ($n = 87$)**	**Median-or-higher TMB ($n = 101$)**	**Below-median TMB ($n = 99$)**	**Median-or-higher TMB ($n = 82$)**
Median PFS (95% CI),[a] months	9.1 (6.9–16.7)	11.2 (8.2–NE)	5.8 (4.1–9.5)	5.5 (2.8–8.3)
Stratified HR (95% CI)[b]	1.17 (0.743–1.841)		0.83 (0.554–1.251)	
1-sided *P* value	0.7505		0.1889	
Median OS (95% CI),[a] months	NE (NE–NE)	NE (NE–NE)	NE (NE–NE)	NE (15.1–NE)
Stratified HR (95% CI)[b]	2.32 (0.828–6.511)		0.73 (0.387–1.380)	
1-sided *P* value	0.9499		0.1663	
ORR, *n* (%)	28 (32.2)	27 (26.7)	26 (26.3)	16 (19.5)
95% CI	22.6–43.1	18.4–36.5	17.9–36.1	11.6–29.7
Unstratified odds ratio (95% CI)[c]	1.301 (0.660–2.563)		1.469 (0.688–3.201)	

[a]CIs were calculated using the Brookmeyer and Crowley method.
[b]Cox proportional hazard model using median-or-higher TMB as the reference group, stratified by ECOG PS (0 vs. 1) and geographical region (US vs. Canada/Western Europe vs. rest of the world).
[c]Odds ratio estimated using the Mantel–Haenszel method.

pathway signatures for fatty acid metabolism ($P = 0.006$), bile acid metabolism ($P = 0.011$), oxidative phosphorylation ($P = 0.017$), adipogenesis ($P = 0.021$), and heme metabolism ($P = 0.043$), which were associated with below-median NLR across the study arms (Supplementary Fig. S3A). Conversely, expression of Hallmark pathway signatures of Myc targets ($P = 0.024$) and G_2–M checkpoint ($P = 0.046$) was associated with median-or-higher NLR irrespective of treatment arm.

Further examination of the gene-expression data using coexpression analyses demonstrated that elevated expression of organic acid metabolic processes ($P = 0.001$), the 26-gene JAVELIN Renal 101 immune signature (ref. 20; $P = 0.021$), and cell-development signatures ($P = 0.041$) were all associated with below-median NLR across the study arms. On examination of the relationship between NLR and angiogenesis signatures (JAVELIN Renal 101 angiogenesis signature and McDermott angiogenesis signature), no relationship was observed (data not shown). Coexpression of cell-cycle ($P = 0.003$), epithelial-to-mesenchymal transition ($P = 0.009$), and neutrophil genes ($P = 0.020$) were associated with the median-or-higher NLR, irrespective of treatment (Supplementary Fig. S3B). This was followed by an examination of the WES data for alterations that might associate with NLR. The exome-wide CNV data obtained in this analysis revealed that below-median NLR was also associated with lower evidence of chromosome instability ($P = 0.0248$; Supplementary Fig. S4; ref. 29). In contrast with the findings for the overall population enrolled in the study (20), analysis of the WES data showed that patients with below-median NLR had higher TMB than patients with median-or-higher NLR ($P = 0.0355$; Supplementary Fig. S5) and a higher frequency of insertions and deletions ($P = 0.0057$ Supplementary Fig. S6). Among commonly observed mutations in RCC, no differences were observed in mutL homolog 1 (*MLH1*) status (copy number, mutations, or expression) or von Hippel-Lindau tumor-suppressor (*VHL*) mutations; however, polybromo 1 (*PBRM1*) was more frequently mutated in the below-median NLR group ($P = 0.0109$; Supplementary Fig. S7). Examination of the WES data for mutational profiles indicated that profiles 12 and 6 (30) were especially strongly associated with below-median NLR (Supplementary Fig. S8). Although the etiology of signature 12 is not fully characterized, the profile is associated with T>C transition mutations. Although somewhat rare across indications, profile 6 is observed in microsatellite instable tumors and has been associated with defects in mismatch repair. Neither PD-L1–positive expression status (1% threshold; $P = 0.4936$; Supplementary Fig. S9) nor the presence of $CD8^+$ cells in various tumor compartments (Supplementary Table S4) was associated with differences in NLR.

Discussion

With an expanding armament of first-line options, reliable pretreatment biomarkers are urgently needed to improve the prognostication of patients with RCC and guide treatment decisions. Biomarkers under investigation for RCC include NLR (3) and the Lung Immune Prognostic Index score (31). Our retrospective analysis is the first study to investigate the association of baseline NLR, dichotomized by the median, with efficacy outcomes in patients receiving an ICI plus TKI combination therapy for advanced RCC. Below-median baseline NLR appeared to be prognostic for better outcomes, although the effect was more pronounced in the sunitinib arm than in the avelumab plus axitinib arm. Multiparametric analyses of tumor samples identified biological differences between tumors with median-or-higher NLR and those with below-median NLR. On the basis of the data from this analysis, NLR appears to be a potential prognostic

biomarker in patients with advanced RCC treated with avelumab plus axitinib or sunitinib.

Our results both confirm and extend the findings of studies that investigated associations of baseline NLR with clinical outcomes in patients with advanced RCC who received ICI or TKI monotherapy (6, 7, 9, 32). Across several studies in RCC, median NLR cutoff values between 2.5 and 5 have been evaluated (6); in the present study, the median NLR was 2.8 in both treatment arms, that is, consistent with previously published studies. In addition, studies of patients with advanced RCC treated with ICIs suggest critical relevance of NLR, but some evidence is conflicting. Although prior studies have shown the importance of changes in NLR on therapy and its association with outcomes, the significance of the baseline measurement varied between retrospective reviews (9, 13). Prospective studies are needed to validate the use of NLR, including potential cutoff values, to determine whether it should be incorporated into prognostication for first-line treatment of advanced RCC in clinical trials or clinical practice.

By combining NLR with TMB, a variable that has predictive value for ICI treatment across multiple cancer types, we observed that PFS and OS were numerically longer in patients in the avelumab plus axitinib arm in those with below-median NLR who had below-median TMB versus those with median-or-higher TMB, whereas no association with TMB was observed in patients with median-or-higher TMB, and no differences were seen in ORR. In contrast, in a retrospective cohort study of patients with various cancers who received ICI treatment, longer PFS and OS and higher response rates were observed in the NLR-low and TMB-high subgroup compared with other subgroups (8).

Nevertheless, the relationship between below-median NLR and favorable outcomes in both treatment arms highlights the potential prognostic value of NLR, whereas its association with key biological characteristics such as TMB, chromosome instability, mutational signatures, pathway activation, cell type–specific signatures, and IMDC risk groups suggests an interrelationship between NLR and the underlying mechanisms influencing clinical outcome. The enrichment of patients with median-or-higher NLR in the IMDC poor-risk group and the elevated metabolic pathways activity (rather than immunomodulatory or receptor signaling [e.g., VEGF in angiogenesis] pathways) are suggestive of linkage with the clinical attributes that compose the IMDC criteria and may, in part, account for the impact of NLR in both treatment arms. In addition, the enrichment of cell-cycle transcriptional programs, such as G_2–M and Myc, seems to reflect the putative "stromal/proliferative" subtype of RCC (cluster 6), which was also enriched in another phase 3 trial in the IMDC poor-risk group and associated with worse PFS in TKI/PD-L1 and TKI arms (30). This phase 3 study also seemed to indicate better clinical outcomes in patients with *PBRM1* alterations (30). The absence of a relationship between NLR and the presence of PD-L1–positive or $CD8^+$ cells in the tumor may indicate that adaptive immunity is not the only driver of response in advanced RCC. However, the cell type–specific transcript results topped by $CD8^+$ cells, M0 macrophages, $CD4^+$ cells, and natural killer cells (among others) suggest that the innate and adaptive immune systems play a role in mediating responses. Further support for enhanced immune recognition as a contributing factor for the differential benefit of patients in these groups is provided by the WES mutation data—most notably, the coincidence of elevated TMB, chromosomal instability, and frequency of insertions and deletions within the below-median NLR population. Mechanistically, insertions and deletions have the potential to alter DNA reading frames and significantly impact resulting protein sequences and their immunogenicity.

In addition to NLR, several other peripheral blood biomarkers have shown an association with prognosis in patients with advanced RCC, including C-reactive protein (CRP), lymphocyte-to-monocyte ratio, and neutrophil-to-eosinophil ratio (NER; refs. 33–35). Recent analyses based on the JAVELIN Renal 101 trial found that both CRP and NER were prognostic in patients with advanced RCC treated with avelumab plus axitinib (36, 37).

In summary, our analysis investigated the association between baseline NLR variations and clinical outcomes in patients with advanced RCC treated with the combination of an ICI and a TKI. We provide additional insights into the utility of NLR as a prognostic biomarker in advanced RCC and correlations with underlying biology in the tumor itself. Our correlative analysis showed an association between NLR and key underlying biological characteristics, which collectively, are both associated with and likely influence clinical outcome. Findings from our analysis provide support for prospective studies to validate baseline NLR, dichotomized by the median or a similar cutoff value, as a prognostic biomarker in patients with advanced RCC.

Authors' Disclosures

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Authors' Contributions

M.A. Bilen: Conceptualization, investigation, methodology, writing–review and editing. **B.I. Rini:** Investigation, writing–review and editing. **M.H. Voss:** Investigation, writing–review and editing. **J. Larkin:** Investigation, writing–review and editing. **J.B.A.G. Haanen:** Investigation, writing–review and editing. **L. Albiges:** Investigation, writing–review and editing. **L.C. Pagliaro:** Investigation, writing–review and editing. **E.G. Voog:** Investigation, writing–review and editing. **E.T. Lam:** Investigation, writing–review and editing. **N. Kislov:** Investigation, writing–review and editing. **B.A. McGregor:** Investigation, writing–review and editing. **A.-K.A. Lalani:** Investigation, writing–review and editing. **B. Huang:** Conceptualization, formal analysis, supervision, investigation, methodology, writing–review and editing. **A. di Pietro:** Conceptualization, supervision, investigation, methodology, writing–review and editing. **S. Krulewicz:** Conceptualization, supervision, investigation, methodology, writing–review and editing. **P.B. Robbins:** Conceptualization, supervision, investigation, methodology, writing–review and editing. **T.K. Choueiri:** Conceptualization, investigation, methodology, writing–review and editing.

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