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Neutrophil-to-Lymphocyte Ratio as a Prognostic Factor of Disease-free Survival in Postnephrectomy High-risk Locoregional Renal Cell Carcinoma: Analysis of the S-TRAC Trial

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ABSTRACT

Purpose: In the S-TRAC trial, adjuvant sunitinib improved disease-free survival (DFS) compared with placebo in patients with locoregional renal cell carcinoma (RCC) at high risk of recurrence. This *post hoc* exploratory analysis investigated the neutrophil-to-lymphocyte ratio (NLR) for predictive and prognostic significance in the RCC adjuvant setting.

Experimental Design: Kaplan–Meier estimates and Cox proportional analyses were performed on baseline NLR and change from baseline at week 4 to assess their association with DFS. Univariate *P* values were two-sided and based on an unstratified log-rank test.

Results: 609 of 615 patients had baseline NLR values; 574 patients had baseline and week 4 values. Sunitinib-treated patients with baseline NLR <3 had longer DFS versus placebo (7.1 vs. 4.7; HR, 0.71; $P = 0.02$). For baseline NLR ≥3, DFS was similar regardless of treatment (sunitinib 6.8 vs. placebo not reached; HR, 1.03; $P = 0.91$). A ≥25% NLR decrease at week 4 was associated with longer DFS versus no change (6.8 vs. 5.3 years; HR, 0.71; $P = 0.01$). A greater proportion of sunitinib-treated patients had ≥25% NLR decrease at week 4 (71.2%) versus placebo (17.4%). Patients with ≥25% NLR decrease at week 4 received a higher median cumulative sunitinib dose (10,137.5 mg) versus no change (8,168.8 mg) or ≥25% increase (6,712.5 mg).

Conclusions: In the postnephrectomy high-risk RCC patient cohort, low baseline NLR may help identify those most suitable for adjuvant sunitinib. A ≥25% NLR decrease at week 4 may be an early indicator of those most likely to tolerate treatment and derive DFS benefit.

Introduction

Cancer development, growth, and metastasis is enabled by certain hallmark capabilities, with the importance of cancer-associated inflammation being increasingly recognized to underpin a variety of essential cancer proliferation attributes that include enabling the supply of several bioreactive molecules to the tumor microenvironment (growth factors, cytokines, and chemokines) that maintain proliferative signaling, proangiogenic factors, and enzymes that facilitate angiogenesis, invasion, immune evasion, and metastasis (1). In general, an active systemic inflammatory response to cancer is associated with poor prognosis. Markers of systemic inflammation, such as C-reactive protein (2), may independently predict patient outcomes.

Neutrophils, the most common form of circulating leukocyte, are the first responsive cell type recruited in the host's innate inflammatory immune response (3). Neutrophils are known to infiltrate many types of tumors including breast (4), prostate (5), non–small cell lung cancer (6), and both locoregional (7) and metastatic renal cell carcinoma (mRCC; refs. 7–10). Tumor-associated neutrophils (TAN) display antitumor and protumor activity and have been termed N1 and N2, respectively (11). Clinical studies indicate that the plasma neutrophil-to-lymphocyte ratio (NLR) can be a universally available and inexpensive prognostic marker, with the majority concluding that a high baseline NLR is correlated with worse prognosis (4–10).

Patients diagnosed with locoregional RCC at high risk of recurrence postnephrectomy represent approximately 15% of the RCC population (12). Over a 5-year period, the recurrence rate in this patient cohort is estimated at 60% (12). Sunitinib, a multitargeted receptor tyrosine kinase inhibitor (TKI), exerts an antiangiogenic effect through inhibition of the VEGF pathway and is a well-established first-line treatment for mRCC (13). Sunitinib was also approved by the FDA for adjuvant RCC treatment in patients at high risk of recurrence postnephrectomy (14) after the publication of S-TRAC trial results, where patients with locoregional RCC at high risk of recurrence postnephrectomy experienced improved disease-free survival (DFS) after adjuvant sunitinib compared with placebo [6.8 vs. 5.6 years; HR, 0.76; 95% confidence interval (CI), 0.59–0.98; $P = 0.03$; ref. 15]. Thus, the sunitinib S-TRAC trial remains the only RCC adjuvant trial to meet its primary endpoint. However, adjuvant treatment-associated increased high-grade adverse events (AE) risk makes optimal patient selection for adjuvant treatment challenging.

A prespecified subgroup analysis of baseline risk factors suggested that a favorable response to sunitinib compared with placebo was more likely in patients with baseline NLR ≤3 (16). This study aimed to evaluate baseline NLR and change in NLR after the first sunitinib dosing cycle for its potential predictive and prognostic ability in postnephrectomy high-risk locoregional nonmetastatic clear cell RCC.

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Translational Relevance

The neutrophil-to-lymphocyte ratio (NLR) has known prognostic ability in numerous cancers, including metastatic renal cell carcinoma (RCC). In patients with locoregional RCC at high risk of recurrence, adjuvant sunitinib prolonged disease-free survival (DFS) compared with placebo (S-TRAC trial); however, identifying those patients who are most likely to tolerate and derive DFS benefit from adjuvant sunitinib is an ongoing challenge. A retrospective exploratory analysis of NLR in the S-TRAC trial population was conducted to seek to aid patient selection to ensure patient benefit and decrease toxicity risk. Sunitinib-treated patients with baseline NLR <3 showed substantially longer DFS compared with placebo. A ≥25% reduction in NLR after the first sunitinib dosing cycle was associated with longer DFS compared with no change or ≥25% increase. Patients with ≥25% reduction in NLR continued on to receive a higher sunitinib dose, suggesting that a reduction in NLR may be an early indicator of treatment success.

Materials and Methods

Study design

S-TRAC was a double-blind, randomized, multicenter phase III trial that randomized 615 patients in a 1:1 ratio to receive either adjuvant sunitinib or placebo (15). The primary endpoint was DFS, defined as recurrence or occurrence of metastasis, a secondary primary malignancy, or death, whichever occurred first (15). This was a *post hoc*, retrospective, exploratory analysis of data from the S-TRAC trial of patients with high-risk locoregional nonmetastatic clear cell RCC. High-risk patients were defined on the basis of The University of California Los Angeles Integrated Staging System (UISS) criteria, as those patients with ≥pT3 and/or N+ tumors. Cumulative dose was defined as the total study dose received over the entire treatment period (extending beyond week 4). S-TRAC was approved by the independent review board or ethics committee at each center. The trial was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in accordance with all International Conference on Harmonization Good Clinical Practice guidelines and applicable local regulatory requirements and laws. All patients provided written informed consent.

Statistical analyses

ROC plots were applied to baseline data to identify optimal NLR cut-off values. Univariable Kaplan–Meier estimates and Cox proportional analyses were performed on baseline and change from baseline NLR data at the end of the first sunitinib dosing cycle (week 4) to assess their association with DFS. *P* values were two-sided and based on an unstratified log-rank test. Multivariate Cox proportional analyses were performed and Kaplan–Meier estimates provided on baseline and change from baseline values at the end of the first sunitinib dosing cycle (week 4). *P* values generated from the multivariate analysis were two-sided and based on a stratified log-rank test.

Data sharing statement

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

Results

Patients

Altogether, 609 of 615 patients had NLR baseline values and 574 had baseline and week 4–paired values. Most patients had baseline neutrophil and lymphocyte counts ≤ upper limit of normal (ULN); only 4.3% (26/609) and 2.0% (12/609) had baseline neutrophil and lymphocyte counts >ULN, respectively. There was no significant difference in median DFS (mDFS) for ≤ULN versus >ULN for baseline neutrophils (6.0 years vs. not reached; HR, 1.42; 95% CI, 0.70–2.86; $P = 0.33$) or lymphocytes (6.0 vs. 6.4 years; HR, 1.33; 95% CI, 0.55–3.21; $P = 0.53$).

NLR cut-off values, based on a ROC plot, were defined as NLR <3 versus ≥3 (**Fig. 1**). Baseline patient demographics were similar between patients with NLR <3 versus ≥3 (**Table 1**). For the NLR <3 and ≥3 groups, patients were predominantly male with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, UISS risk group T3 high, and Fuhrman grade 3–4 (**Table 1**).

Baseline NLR as a prognostic marker

In the overall population, mDFS was shorter in the NLR <3 group versus the NLR ≥3 group (5.79 years vs. not reached; HR, 1.39; 95% CI, 1.01–1.90; $P = 0.04$); however, patients with baseline NLR <3 who received sunitinib, had longer mDFS compared with placebo (7.1 vs. 4.7 years; HR, 0.71; 95% CI, 0.54–0.94; $P = 0.02$; **Fig. 2A**). For patients with baseline NLR ≥3, mDFS was similar regardless of treatment (HR, 1.03; 95% CI, 0.59–1.81; $P = 0.91$; **Fig. 2B**).

Change from baseline NLR as a prognostic and predictive marker

In the overall population, a ≥25% decrease in NLR at week 4 was associated with longer DFS versus no change (6.8 vs. 5.3 years; HR, 0.71; 95% CI, 0.54–0.92; $P = 0.01$; **Fig. 3**). There was no statistically significant difference in mDFS in patients with a ≥25% increase in NLR

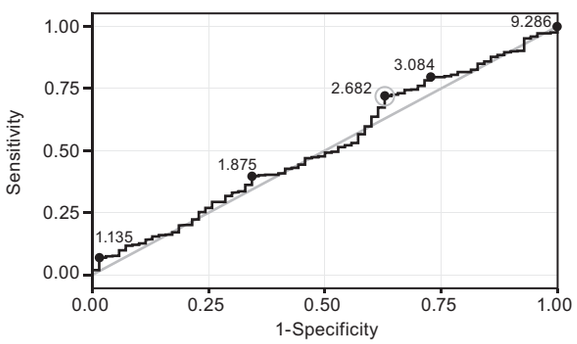

Figure 1.
ROC plot of baseline neutrophil-to-lymphocyte ratio.

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Table 1. Patient demographics and baseline characteristics, overall population.

	NLR <3, *N* = 469	NLR ≥3, *N* = 140
Median age, years (range)	56.0 (21–83)	59.5 (25–81)
Sex, *n* (%)		
Male	335 (71.4)	111 (79.3)
Female	134 (28.6)	29 (20.7)
ECOG PS, *n* (%)		
0	346 (73.8)	98 (70.0)
1	121 (25.8)	40 (28.6)
2	0	1 (0.7)
NR	2 (0.4)	1 (0.7)
UISS risk group, *n* (%)		
T3 low[a]	171 (36.5)	55 (39.3)
T3 high[b]	257 (54.8)	70 (50.0)
T4/any T N+[c]	41 (8.8)	15 (10.7)
Fuhrman grade, *n* (%)		
1–2	178 (37.9)	48 (34.2)
3–4	290 (61.8)	91 (65.0)
NR	1 (0.2)	1 (0.7)

Abbreviation: NR, not reported.

[a]T3, no or undetermined nodal involvement, no metastasis, any Fuhrman grade, ECOG PS 0 or Fuhrman grade 1, ECOG PS 1.

[b]T3, no or undetermined nodal involvement, no metastasis, Fuhrman grade ≥2, ECOG PS ≥1.

[c]T4 or any T with nodal involvement, no metastasis, any Fuhrman grade, any ECOG PS.

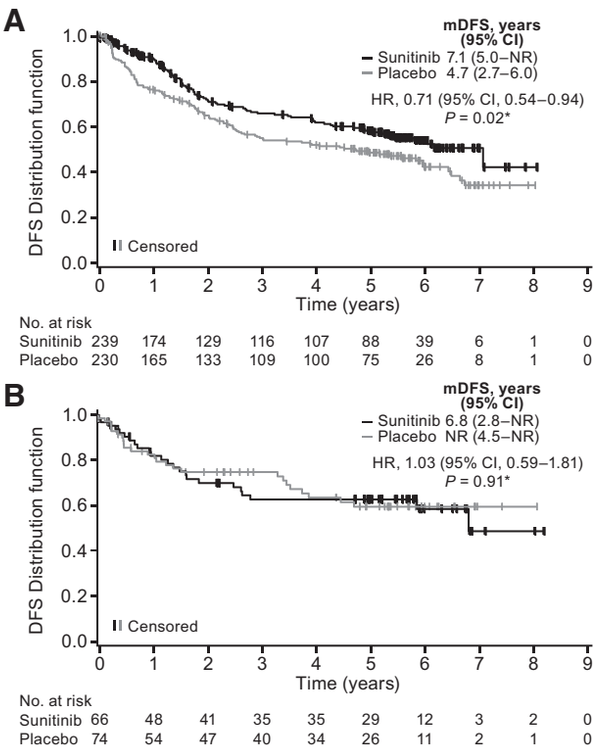

Figure 2.

Kaplan–Meier plot of DFS with sunitinib versus placebo, by baseline neutrophil-to-lymphocyte ratio <3 (**A**) and ≥3 (**B**); intent-to-treat population. *, Two-sided, unstratified log-rank test. CI, confidence interval; NR, not reached.

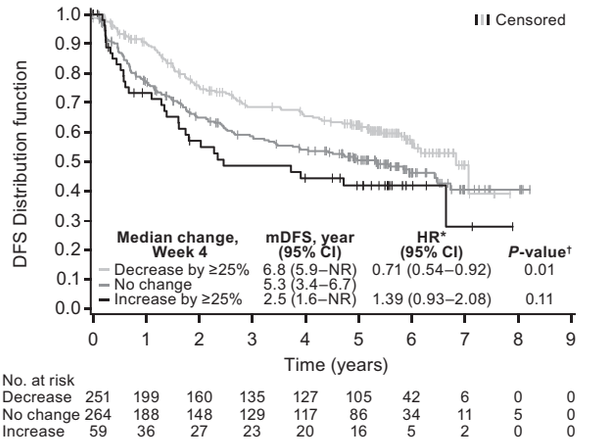

Figure 3.

Kaplan–Meier plot of DFS by change from baseline neutrophil-to-lymphocyte ratio stratified by UISS high-risk group, overall population. *, no change at week 4. †, Two-sided stratified log-rank test. CI, confidence interval; NR, not reached.

at week 4 versus no change (2.5 vs. 5.3 years; HR, 1.39; 95% CI, 0.93–2.08; $P = 0.11$). A significantly greater proportion of sunitinib-treated patients had a ≥25% decrease in NLR ($P < 0.0001$) at week 4 versus placebo (**Table 2**). Patients with a ≥25% decrease in NLR at week 4 also continued to tolerate and receive a higher median cumulative dose of sunitinib than those with no change or ≥25% increase (**Table 2**).

Multivariate analysis

Multivariate analyses confirmed that baseline NLR <3 versus ≥3 (HR, 1.61; 95% CI, 1.15–2.26; $P = 0.006$) was an independent predictor of DFS (**Table 3**). Other baseline factors independently associated with improved DFS were treatment (sunitinib vs. placebo, $P = 0.0204$), UISS (other vs. T3 low, $P = 0.0059$), and Fuhrman grade (1 and 2 vs. 3 and 4, $P = 0.0070$; **Table 3**). The multivariate analysis indicated that there was some additional value in the use of NLR following adjustment for UISS staging (**Table 3**).

Discussion

Identifying patients with RCC at high risk of recurrence post-nephrectomy who are most likely to benefit from adjuvant treatment remains a challenging area of unmet medical need. It is equally important to avoid potential toxicity in patients least likely to derive adjuvant treatment DFS benefit, at baseline or early in treatment. Our

Table 2. Patients with changes in neutrophil-to-lymphocyte ratio at week 4 and cumulative median total dose by treatment group.

	≥25% decrease	No change	≥25% increase
Patients, *n* (%)			
Sunitinib	200 (71.2)	67 (23.8)	14 (5.0)
Placebo	51 (17.4)	197 (67.2)	45 (15.4)
P-value vs. placebo	<0.0001	—	—
Cumulative median total dose at week 4, mg			
Sunitinib	10,137.5	8,168.8	6,712.5
Placebo	12,600.0	12,250.0	10,025.0

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Table 3. Multivariate Cox proportional analysis of disease-free survival and baseline characteristics.

	HR (95% CI)	*P*-value
UISS, other[a] vs. T3 low	1.83 (1.19–2.81)	0.0059
Neutrophil-to-lymphocyte ratio, <3 vs. ≥3	1.61 (1.15–2.26)	0.0060
Fuhrman grade, 1 and 2 vs. 3 and 4	0.69 (0.52–0.90)	0.0070
Treatment, sunitinib vs. placebo	0.74 (0.58–0.96)	0.0204
Platelet-to-lymphocyte ratio, <140 vs. ≥140	0.79 (0.61–1.03)	0.0809
Age, ≥65 vs. <65 years	1.26 (0.95–1.66)	0.1109
Sex, female vs. male	1.18 (0.87–1.60)	0.2924
BMI, <25 vs. ≥25	0.88 (0.68–1.15)	0.3532
Baseline ECOG PS, 0 vs. >0	0.91 (0.67–1.23)	0.5309
UISS, T3 high vs. T3 low	1.07 (0.79–1.45)	0.6457

Abbreviations: BMI, body mass index; CI, confidence interval.
[a]T4, N0 or NX, M0, any Fuhrman grade, and any ECOG status or any T, N1–2, M0, any Fuhrman grade, and any ECOG status.

study suggests that patients with high-risk locoregional RCC with a baseline NLR <3 postnephrectomy were most likely to have a beneficial DFS response to adjuvant sunitinib. A 25% decrease in NLR at week 4 may further refine the patient group most likely to continue to tolerate a clinically beneficial sunitinib dose and gain DFS benefit. In this respect, NLR appears to be functioning as a predictive rather than prognostic factor in this population.

Of the completed RCC adjuvant trials, S-TRAC is the only trial to meet its primary endpoint (15). In the intent-to-treat population, which was inclusive of any baseline NLR, adjuvant sunitinib increased mDFS by 1.2 years compared with placebo (6.8 vs. 5.6 years; HR, 0.76; ref. 15). In this analysis, although NLR <3 was associated with a shorter mDFS compared with NLR ≥3 in the overall population, there was a clear mDFS benefit for patients with a low baseline NLR who received sunitinib; mDFS increased from 4.7 years with placebo to 7.1 years with sunitinib, representing an increase of 2.4 years (HR, 0.71). Furthermore, a clear and sustained separation was evident between the NLR ≥3 and <3 Kaplan–Meier curves. A pooled analysis of the S-TRAC, ASSURE (sorafenib or sunitinib vs. placebo), and PROTECT (pazopanib vs. placebo) trials reported that in intermediate/high-risk patients, there was no consistent improvement in survival associated with VEGFR-targeted adjuvant treatment (17). Differences in trial design, dosing strategy, and patient risk categories may have contributed to the apparent discrepancy in adjuvant trial results (18). Compared with other completed trials, patients in S-TRAC were at a higher risk of recurrence, with high-risk defined as T3, N0, or Nx, any Fuhrman grade + any ECOG PS; or any T, N+, any Fuhrman grade + any ECOG PS (15). Our study supports the premise that adjuvant sunitinib treatment should only be considered in these higher-risk patients and that NLR may be an inexpensive, easily accessible tool to help guide optimal patient selection. In addition, our analysis highlights the importance of cumulative dose in relation to clinical benefit. The cumulative dose represented that of the entire treatment period, that is, extending beyond analysis at week 4, and was therefore related to total treatment duration. No association was observed with the average daily sunitinib dose, which was likely due to a longer treatment duration in patients who did not discontinue treatment due to AEs or other reasons. Consistently, a pooled analysis of adjuvant RCC trials found that patients who were able to start and maintain a full dose regimen were most likely to derive DFS benefit (17). In the S-TRAC population, patients with a ≥25% decrease in NLR after 4 weeks had a longer mDFS and could tolerate a higher median cumulative dose of sunitinib, than patients who had no change or a ≥25% increase in NLR.

Baseline, and change from baseline, NLR are predictive of treatment outcomes in mRCC. A systematic review and meta-analysis of TKI-treated patients with mRCC found that a high baseline NLR was associated with shorter median progression-free survival (PFS) and median overall survival (OS; ref. 8). A pooled analysis of sunitinib randomized clinical trials reported that low baseline NLR (≤3) and a decrease in NLR (25%–50%) were associated with improved PFS, OS, and objective response rate (9). A ≥25% increase in NLR has also been associated with inferior mRCC clinical outcomes (8, 10); however, in the adjuvant setting, no significant association between outcomes and baseline NLR ≥3 or ≥25% increases were observed. These differences may be driven by the primary cause of the inflammation.

Few studies have examined NLR in the adjuvant setting. A retrospective analysis of patients with stage II/III gastric cancer who received adjuvant chemotherapy found that an increase in NLR during adjuvant treatment was associated with a poorer prognosis (19). The precise mechanisms underlying NLR as a prognostic or predictive biomarker are unclear, but may represent a dynamic relationship between the NLR and the potential immunomodulatory effects of the treatment. Our study supports an immunomodulatory effect of sunitinib, with a greater proportion of patients who received sunitinib showing a reduction in NLR versus those who received placebo. In mRCC, TANs are often associated with myeloid-derived suppressor cells (MDSC) and can release proangiogenic factors, such as matrix metallopeptidases and IL8, that may promote sunitinib resistance (20). As RCC progresses, the accumulation of these and other protumor factors released by N2 TANs, such as reactive oxygen species, cytokines, and chemokines, may promote survival and growth of the tumor (21). Inflammation in mRCC is attributable to the tumor burden; hence an increase in NLR, which may be driven by a high neutrophil count, was associated with inferior clinical outcomes (8, 10). In the adjuvant setting, NLR may instead be driven by postoperative events and/or the body's response to the primary tumor burden. In S-TRAC, adjuvant treatment initiation was required to start 3–12 weeks after nephrectomy (15). The postnephrectomy status of these patients may mean that some neutrophils were sequestered into the surgical bed while some lymphocytes were undoubtedly sequestered into the tumor tissue, both of which could affect the ratio. In a RCC model, sunitinib treatment before resection led to the expansion of tumor-infiltrating lymphocytes (TIL), which was also associated with a decrease in the MDSC content of the tumor (22). The reduction in NLR in response to adjuvant sunitinib treatment may therefore be driven by an increase in TILs. Given the role of MDSCs in promoting tumor growth and sunitinib resistance, this suggests a potential rationale for the use of NLR as a prognostic and predictive biomarker.

The multivariate analysis of baseline factors, including other known risk variables for RCC, confirmed that NLR <3 versus ≥3 was independently associated with longer DFS. In order of significance, UISS other versus T3, NLR <3 versus ≥3, sunitinib treatment versus placebo, and Fuhrman grades 1/2 versus 3/4 were all associated with longer DFS. The multivariate analysis suggested there was additional value of NLR even after adjustment for UISS staging. The definition of high-risk patients is important when considering which patients may benefit from adjuvant treatment. In this respect, it is noteworthy that the S-TRAC trial used modified UISS criteria to stratify patients, which included patients of any Fuhrman grade and any ECOG PS. Interestingly, neutrophil count, but not NLR, is part of one of the most common prognostic models used to stratify patients with mRCC into risk groups, the International Metastatic RCC Database

Consortium (IMDC) model. A retrospective analysis of TKI-treated patients suggested that the accuracy of the IMDC model could be improved by including NLR instead of absolute neutrophil count (23), emphasizing the potential significance of NLR as a prognostic marker in TKI-/sunitinib-treated patients.

In the current absence of reliable biomarkers, baseline NLR and changes in NLR upon treatment both represent universally accessible, routinely performed, and inexpensive predictive and potentially prognostic factors, in this setting. Exploration of other predictive factors may help further refine adjuvant patient selection. A prospectively designed analysis of immune tissue biomarkers in the S-TRAC trial population reported that a greater $CD8^+$ T-cell density in tumor tissue was associated with a longer DFS in patients who received sunitinib (24). A validated 16-gene recurrence score (RS) assay, developed to predict the likelihood of recurrence postnephrectomy in patients with locoregional RCC (25), was further validated in a prospectively designed analysis of the S-TRAC population (26). The RS successfully predicted time to recurrence, DFS, and renal cancer–specific survival in both placebo and sunitinib arms (26). In addition, a pharmacogenomic analysis of the S-TRAC trial found that SNPs in the *VEGFR1* and *VEGFR2* genes were associated with longer DFS in patients receiving adjuvant sunitinib (27). Although each of these approaches is promising, confirmatory studies are necessary.

This is the first study to provide an in-depth analysis of NLR as a predictive and prognostic factor in the adjuvant RCC setting. However, this study is not without limitations. This was a retrospective study and all analyses were exploratory. Our analysis did not categorize changes in NLR beyond ≥25% increase or decrease. In contrast to a 25%–50% NLR decrease from baseline, a >75% decrease was not associated with improved outcomes in patients with mRCC (10). This may have been due to relatively small patient numbers or high baseline NLR, or may represent a trade-off between the protumor and antitumor effects of TANs. Tolerance of adjuvant sunitinib was not formally examined in this exploratory study, but was inferred from the total cumulative dose and therefore treatment duration. Reasons for discontinuation of adjuvant treatment or dose reductions due to AEs could therefore not be assessed. Our study did not examine prenephrectomy neutrophil and lymphocyte counts. Preoperative NLR and platelet-to-lymphocyte ratio have been reported to have prognostic value in several histologic subtypes of RCC (28) including Xp11.2 translocation/*TFE3* gene fusions RCC (29). This study did not examine the potential impact of time since nephrectomy and baseline NLR; however, all patients initiated adjuvant treatment 3–12 weeks postnephrectomy as per predefined S-TRAC protocol inclusion criteria. Finally, data were not available on whether any patients received postoperative blood transfusions, which may have interfered with the recorded NLR. Nevertheless, given the increasingly minimally invasive laparoscopic nature of the modern nephrectomy procedure, this number of patients is likely to have been low.

Conclusions

In patients with locoregional clear cell RCC at high risk of recurrence postnephrectomy, both baseline NLR <3 and a 25% decrease in NLR at 4 weeks appear to be early predictors of those patients most likely to benefit from adjuvant sunitinib. NLR changes at the end of the first sunitinib dosing cycle appeared to separate those patients most likely to maintain their dose of and respond to adjuvant sunitinib, from those with RCC who seem least likely to benefit. Monitoring NLR might therefore help reduce potentially avoidable toxicity risk early in this part of the high-risk locoregional RCC patient journey. Further investigation in prospectively designed trials is warranted.

Disclosure of Potential Conflicts of Interest

A. Patel reports personal fees and nonfinancial support from Pfizer (Global Steering Committee consulting fees and manuscript preparation support) during the conduct of the study. A. Ravaud reports personal fees and nonfinancial support from Pfizer during the conduct of the study; grants, personal fees, and nonfinancial support from Pfizer, grants and nonfinancial support from Merck GA, personal fees and nonfinancial support from Novartis, MSD, AstraZeneca, Ipsen, and Roche outside the submitted work. R.J. Motzer reports grants and personal fees from Pfizer [consulting fees to author and grant to employer (MSK)] during the conduct of the study; grants and personal fees from Eisai [consulting fees to author and grant to employer (MSK)], Genentech/Roche [consulting fees to author and grant to employer (MSK)], Novartis [consulting fees to author and grant to employer (MSK)], Exelixis [consulting fees to author and grant to employer (MSK)], personal fees from Lilly Oncology (consulting author), grants from Bristol Myers Squibb (clinical trial support to employer), and personal fees from Incyte (consulting to author) outside the submitted work. A.J. Pantuck reports grants from Pfizer (UCLA for being a site for the S-TRAC study) during the conduct of the study and personal fees from Pfizer (consulting) outside the submitted work. M. Staehler reports grants, personal fees, and nonfinancial support from Pfizer during the conduct of the study; grants, personal fees, and nonfinancial support from Pfizer, GlaxoSmithKline, Novartis, Bayer, and Roche, and grants and personal fees from Exelixis outside the submitted work. B. Escudier reports personal fees from Pfizer during the conduct of the study and personal fees from BMS, Ipsen, and Roche outside the submitted work. J.-F. Martini reports personal fees from Pfizer Inc (employment) outside the submitted work. M.J. Lechuga reports personal fees from Pfizer during the conduct of the study and other from Pfizer (stocks) outside the submitted work. X. Lin reports other from Pfizer Inc. (employment with Pfizer) during the conduct of the study. D.J. George reports grants from Acerta Pharmaceuticals, Novartis, Calithera, and other from American Association for Cancer Research (Sr. Editor); grants and personal fees from Astellas; personal fees from AstraZeneca and Axess Oncology; grants and personal fees from Bayer H/C Pharma, Pfizer; grants, personal fees, and other from BMS (Steering Committee), and other from Capio Biosciences (scientific advisory board), personal fees from EMD Serono, Flatiron, Ipsen, Merck Sharp & Dohme, Michael J Hennessey, Myovant Sciences, Physician Education Resource, UroGPO, UroToday, and Vizuri Health Sciences; grants and personal fees from Exelixis and Sanofi; grants, personal fees, and other from Janssen Pharma (IDMC); and other from Millennium Med Pub (Co-Editor-in-Chief) and Modra Pharma (advisory board), NCI GU (Steering Committee Mbr) and Nektar Therapeutics (Steering Committee Mbr) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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