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Neutrophil-to-Lymphocyte Ratio as a Prognostic Factor of Disease-Free Survival in Post-Nephrectomy High-Risk Loco-Regional 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 loco-regional renal cell carcinoma (RCC) at high risk of

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Drafting of the manuscript: All authors

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Supervision: Jean-François Martini, Mariajose Lechuga, Xun Lin

Other (specify): None

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 de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) 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 de-identified 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.

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: 609/615 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 post-nephrectomy 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.

Keywords

Adjuvant; NLR; Prognostic; Renal cell carcinoma; Sunitinib

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; pro-angiogenic 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 loco-regional (7) and metastatic renal cell carcinoma (mRCC) (7–10). Tumor-associated neutrophils (TANs) display anti-tumor and pro-tumor 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 loco-regional RCC at high risk of recurrence post-nephrectomy 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 multi-targeted receptor tyrosine kinase inhibitor (TKI), exerts an anti-angiogenic effect through inhibition of the VEGF pathway and is a well-established first-line treatment for mRCC (13). Sunitinib was also approved by the US Food and Drug Administration for adjuvant RCC treatment in patients at high risk of recurrence post-nephrectomy (14) after the publication of S-TRAC trial results, where patients with loco-regional RCC at high risk of recurrence post-nephrectomy, 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; $P = 0.03$) (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 (AEs) risk makes optimal patient selection for adjuvant treatment challenging.

A pre-specified 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 post-nephrectomy high-risk loco-regional non-metastatic clear-cell RCC.

Patients 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 S-TRAC 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 loco-regional non-metastatic clear cell RCC. High-risk patients were defined based on 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

Receiver operating characteristic (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 dosing sunitinib 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 dosing sunitinib cycle (week 4). *P*-values generated from the multivariate analysis were two-sided and based on a stratified log-rank test.

Results

Patients

Altogether, 609/615 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 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 on in treatment. Our study suggests that high-risk loco-regional RCC patients with a baseline NLR <3 post-nephrectomy 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) (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, i.e. 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 (mPFS) and median overall survival (OS) (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 (MDSCs) and can release pro-angiogenic factors, such as matrix metallopeptidases and interleukin-8, that may promote sunitinib resistance (20). As RCC progresses, the accumulation of these and other pro-tumor 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 post-operative 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 post-nephrectomy 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 (TILs), 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 post-nephrectomy in patients with loco-regional 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). Additionally, a pharmacogenomic analysis of the S-TRAC trial found that single-nucleotide polymorphisms 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 pro- and anti-tumor 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 pre-nephrectomy neutrophil and lymphocyte counts. Preoperative NLR and platelet-to-lymphocyte ratio have been reported to have prognostic value in several histological 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 post nephrectomy as per pre-defined STRAC protocol inclusion criteria. Finally, data were not available on whether any patients received post-operative 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 loco-regional clear-cell RCC at high risk of recurrence post-nephrectomy, 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 loco-regional RCC patient journey. Further investigation in prospectively designed trials is warranted.

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Disclosure of Potential Conflicts of Interest

Anup Patel received fees for consulting and serving on a steering committee from Pfizer.

Alain Ravaud receives fees for serving on advisory boards from Pfizer, Novartis, GlaxoSmithKline, Bristol-Myers Squibb, and Roche; lecture fees from Pfizer, Novartis, and GlaxoSmithKline; travel support from Pfizer, Novartis, GlaxoSmithKline, Bristol-Myers Squibb, and Merck Sharp & Dohme; and grant support from Pfizer and Novartis. Robert J. Motzer receives consulting fees from Pfizer, Eisai, Novartis, Merck, Genentech/Roche, Incyte, Lilly Oncology, and Exelixis; and clinical trial support to his institution from Pfizer, Eisai, Novartis, Bristol-Myers Squibb, Genentech/Roche, GlaxoSmithKline, and Exelixis. Allan J. Pantuck receives fees for consulting from Pfizer. Michael Staehler receives grant support and fees for serving on advisory boards for Pfizer, GlaxoSmithKline, Novartis, Bayer, Exelixis, and Roche; and consulting fees, honoraria, and travel support from Pfizer, GlaxoSmithKline, Novartis, Bayer, and Roche. Bernard Escudier receives fees for serving on advisory boards from Pfizer, Novartis, Bristol-Myers Squibb, Exelixis, and Roche; and lecture fees from Pfizer and Novartis. Jean-François Martini, Mariajose Lechuga, and Xun Lin are employees of Pfizer Inc. Daniel J. George receives honoraria and consulting fees from Sanofi, Exelixis, and Bayer; consulting fees from Merck and Sanofi; grants from Genentech/Roche, Novartis, Astellas, Celldex, and Acerta; and grants and consulting fees from Exelixis, Janssen, Pfizer, Innocrin Pharma, and Bristol-Myers Squibb.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74. [PubMed: 21376230]
2. Zhou L, Cai X, Liu Q, Jian ZY, Li H, Wang KJ. Prognostic role of C-reactive protein in urological cancers: a meta-analysis. Sci Rep 2015;5:12733. [PubMed: 26235332]
3. Selders GS, Fetz AE, Radic MZ, Bowlin GL. An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration. Regen Biomater 2017;4:55–68. [PubMed: 28149530]
4. Guo W, Lu X, Liu Q, Zhang T, Li P, Qiao W, et al. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for breast cancer patients: an updated meta-analysis of 17079 individuals. Cancer Med 2019;8:4135–48. [PubMed: 31197958]
5. Peng H, Luo X. Prognostic significance of elevated pretreatment systemic inflammatory markers for patients with prostate cancer: a meta-analysis. Cancer Cell Int 2019;19:70. [PubMed: 30962764]
6. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176–81. [PubMed: 28838390]
7. Nunno VD, Mollica V, Gatto L, Santoni M, Cosmai L, Porta C, et al. Prognostic impact of neutrophil-to-lymphocyte ratio in renal cell carcinoma: a systematic review and meta-analysis. Immunotherapy 2019;11:631–43. [PubMed: 30943858]
8. Semeniuk-Wojtas A, Lubas A, Stec R, Syrylo T, Niemczyk S, Szczylik C. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein as new and simple prognostic factors in patients with metastatic renal cell cancer treated with tyrosine kinase inhibitors: A systemic review and meta-analysis. Clin Genitourin Cancer 2018;16:e685–e93. [PubMed: 29454639]
9. Tannir NM, Figlin RA, Gore ME, Michaelson MD, Motzer RJ, Porta C, et al. Long-term response to sunitinib treatment in metastatic renal cell carcinoma: a pooled analysis of clinical trials. Clin Genitourin Cancer 2017;S1558–7673:30171–4.
10. Templeton AJ, Knox JJ, Lin X, Simantov R, Xie W, Lawrence N, et al. Change in neutrophil-to-lymphocyte ratio in response to targeted therapy for metastatic renal cell carcinoma as a prognosticator and biomarker of efficacy. Eur Urol 2016;70:358–64. [PubMed: 26924770]
11. Uribe-Querol E, Rosales C. Neutrophils in cancer: two sides of the same coin. J Immunol Res 2015;2015:983698. [PubMed: 26819959]

12. Lam JS, Shvarts O, Leppert JT, Pantuck AJ, Figlin RA, Belldegrun AS. Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol 2005;174:466–72; discussion 72; quiz 801. [PubMed: 16006866]
13. Moran M, Nickens D, Adcock K, Bennetts M, Desscan A, Charnley N, et al. Sunitinib for metastatic renal cell carcinoma: A systematic review and meta-analysis of real-world and clinical trials data. Target Oncol 2019;14:405–16. [PubMed: 31301015]
14. US Food and Drug Administration. FDA approves sunitinib malate for adjuvant treatment of renal cell carcinoma. Bethesda, MD: US FDA; 2018 Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sunitinib-malate-adjuvant-treatment-renal-cell-carcinoma. Accessed November 22, 2019.
15. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 2016;375:2246–54. [PubMed: 27718781]
16. Motzer RJ, Ravaud A, Patard JJ, Pandha HS, George DJ, Patel A, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. Eur Urol 2018;73:62–8. [PubMed: 28967554]
17. Sun M, Marconi L, Eisen T, Escudier B, Giles RH, Haas NB, et al. Adjuvant vascular endothelial growth factor-targeted therapy in renal cell carcinoma: a systematic review and pooled analysis. Eur Urol 2018;74:611–20. [PubMed: 29784193]
18. Figlin RA, Leibovich BC, Stewart GD, Negrier S. Adjuvant therapy in renal cell carcinoma: does higher risk for recurrence improve the chance for success? Ann Oncol 2018;29:324–31. [PubMed: 29186296]
19. Mori M, Shuto K, Kosugi C, Narushima K, Hayashi H, Matsubara H, et al. An increase in the neutrophil-to-lymphocyte ratio during adjuvant chemotherapy indicates a poor prognosis in patients with stage II or III gastric cancer. BMC Cancer 2018;18:1261. [PubMed: 30558575]
20. Finke J, Ko J, Rini B, Rayman P, Ireland J, Cohen P. MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy. Int Immunopharmacol 2011;11:856–61. [PubMed: 21315783]
21. Wu L, Saxena S, Awaji M, Singh RK. Tumor-associated neutrophils in cancer: going pro. Cancers (Basel) 2019;11:564–84.
22. Guislain A, Gadiot J, Kaiser A, Jordanova ES, Broeks A, Sanders J, et al. Sunitinib pretreatment improves tumor-infiltrating lymphocyte expansion by reduction in intratumoral content of myeloid-derived suppressor cells in human renal cell carcinoma. Cancer Immunol Immunother 2015;64:1241–50. [PubMed: 26105626]
23. Chrom P, Stec R, Bodnar L, Szczylik C. Incorporating neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in place of neutrophil count and platelet count improves prognostic accuracy of the International Metastatic Renal Cell Carcinoma Database Consortium Model. Cancer Res Treat 2018;50:103–10. [PubMed: 28253564]
24. George DJ, Martini JF, Staehler M, Motzer RJ, Magheli A, Escudier B, et al. Immune biomarkers predictive for disease-free survival with adjuvant sunitinib in high-risk locoregional renal cell carcinoma: from randomized phase III S-TRAC study. Clin Cancer Res 2018;24:1554–61. [PubMed: 29374054]
25. Rini B, Goddard A, Knezevic D, Maddala T, Zhou M, Aydin H, et al. A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. Lancet Oncol 2015;16:676–85. [PubMed: 25979595]
26. Rini BI, Escudier B, Martini JF, Magheli A, Svedman C, Lopatin M, et al. Validation of the 16-gene recurrence score in patients with locoregional, high-risk renal cell carcinoma from a phase III trial of adjuvant sunitinib. Clin Cancer Res 2018;24:4407–15. [PubMed: 29773662]
27. Cella D, Grunwald V, Escudier B, Hammers HJ, George S, Nathan P, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol 2019;20:297–310. [PubMed: 30658932]

28. Keskin S, Keskin Z, Taskapu HH, Kalkan H, Kaynar M, Poyraz N, et al. Prognostic value of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, and multiphasic renal tomography findings in histological subtypes of renal cell carcinoma. BMC Urol 2014;14:95. [PubMed: 25427576]

29. Agizamhan S, Qu F, Liu N, Sun J, Xu W, Zhang L, et al. Preoperative neutrophil-to-lymphocyte ratio predicts the surgical outcome of Xp11.2 translocation/TFE3 renal cell carcinoma patients. BMC Urol 2018;18:60. [PubMed: 29890986]

Translational Relevance

The neutrophil-to-lymphocyte ratio (NLR) has known prognostic ability in numerous cancers, including metastatic renal cell carcinoma (RCC). In patients with loco-regional 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.

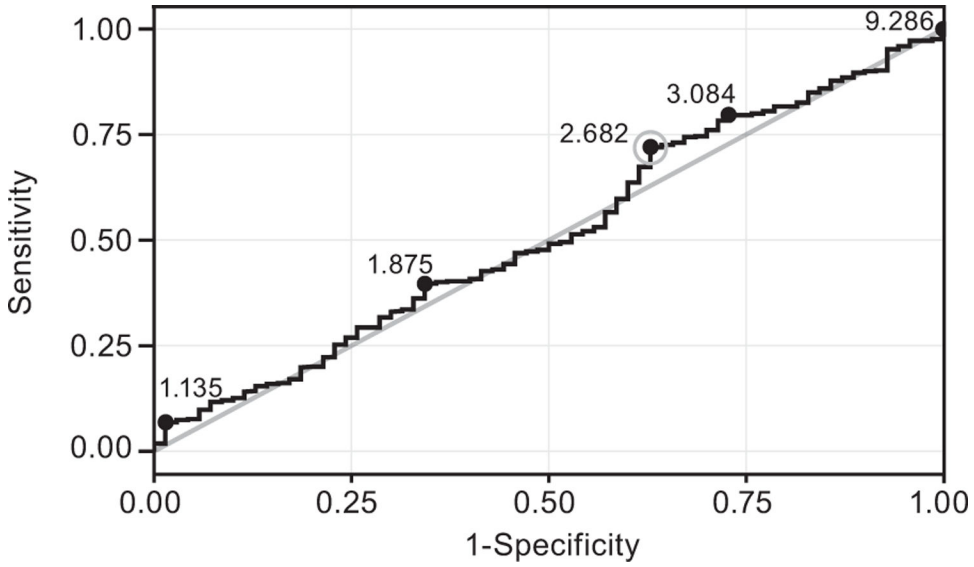

Figure 1.
ROC (receiver operating characteristic) plot of baseline neutrophil-to-lymphocyte ratio.

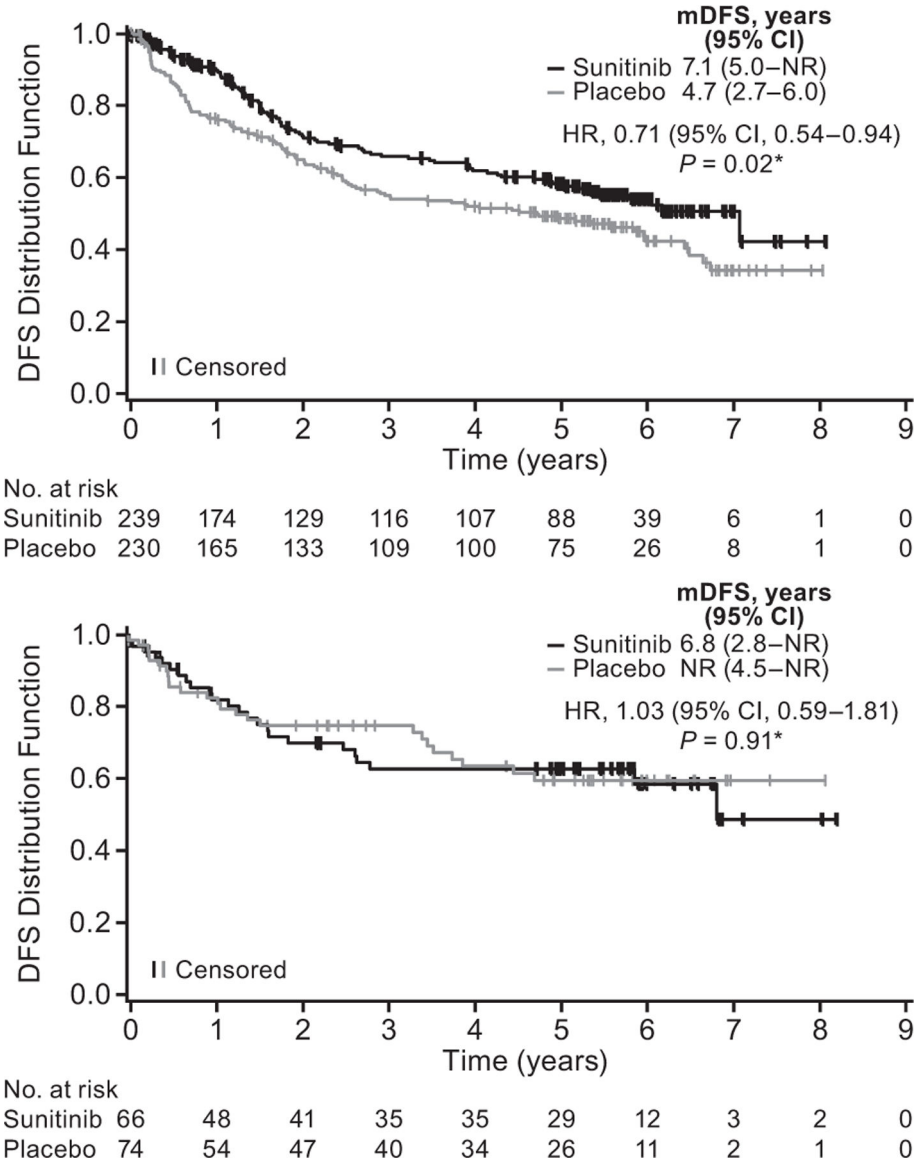

Figure 2.

Kaplan–Meier plot of disease-free survival with sunitinib versus placebo, by baseline neutrophil-to-lymphocyte ratio (A) <3 and (B) ≥3; intent-to-treat population.

*2-sided, unstratified log-rank test.

Abbreviations: CI, confidence interval; NR, not reached.

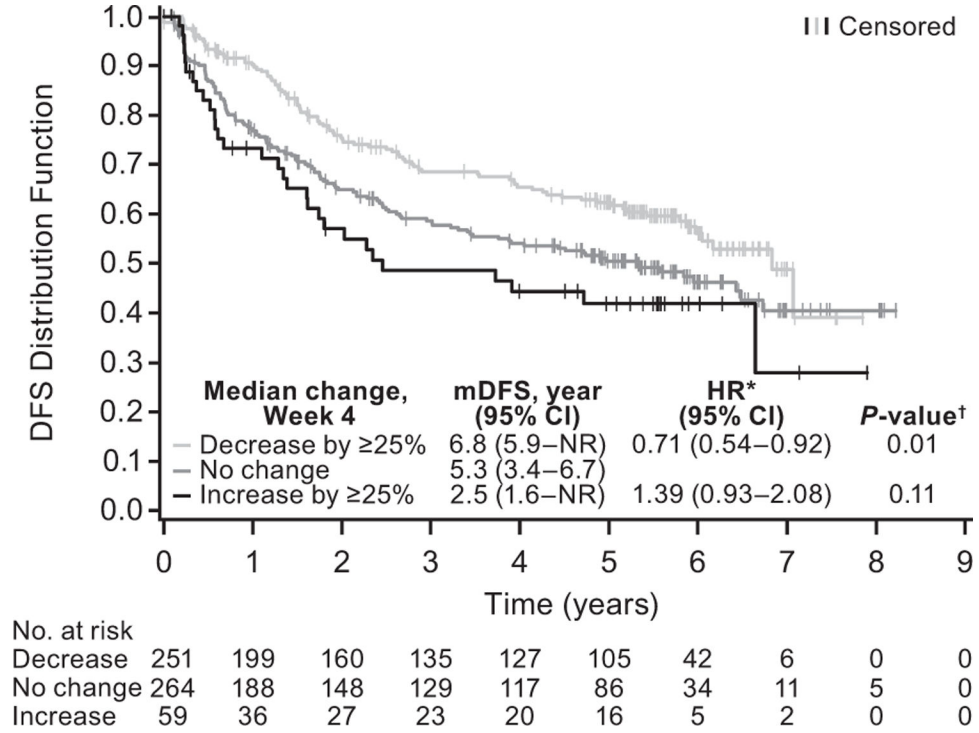

Figure 3.

Kaplan–Meier plot of median disease-free survival by change from baseline neutrophil-to-lymphocyte ratio stratified by UISS high-risk group, overall population.

*vs. no change at week 4.

†2-sided stratified log-rank test.

Abbreviations: CI, confidence interval; NR, not reached.

Table 1.

Patient demographics and baseline characteristics, overall population.

	NLR <3 ***N* = 469**	**NLR ≥3** ***N* = 140**
Median age, yrs (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)

[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.

Abbreviation: NR, not reported.

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

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

[a]T4, N0 or NX, M0, any Fuhrman's grade, and any ECOG status or Any T, N1–2, M0, any Fuhrman's grade, and any ECOG status.

Abbreviations: BMI, body mass index; CI, confidence interval.