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European Association of Urology

Kidney Cancer

Change in Neutrophil-to-lymphocyte Ratio in Response to Targeted Therapy for Metastatic Renal Cell Carcinoma as a Prognosticator and Biomarker of Efficacy

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Article info

Article history:
Accepted February 9, 2016

Associate Editor:
James Catto

Keywords:
Change
Conversion
Renal cell carcinoma
Prognosis
Neutrophil-to-lymphocyte ratio
Targeted therapy

Abstract

Background: Neutrophil-to-lymphocyte ratio (NLR), if elevated, is associated with worse outcomes in several malignancies.
Objective: Investigation of NLR at baseline and during therapy for metastatic renal cell carcinoma.
Design, setting, and participants: Retrospective analysis of 1199 patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC cohort) and 4350 patients from 12 prospective randomized trials (validation cohort).
Intervention: Targeted therapies for metastatic renal cell carcinoma.
Outcome measurements and statistical analysis: NLR was examined at baseline and 6 (± 2) wk later. A landmark analysis at 8 wk was conducted to explore the prognostic value of relative NLR change on overall survival (OS), progression-free survival (PFS), and objective response rate using Cox or logistic regression models, adjusted for variables in IMDC score and NLR values at baseline.
Results and limitations: Higher NLR at baseline was associated with shorter OS and PFS (Hazard Ratios [HR] per 1 unit increase in log-transformed NLR = 1.69 [95% confidence interval {CI} = 1.46–1.95] and 1.30 [95% CI = 1.15–1.48], respectively). Compared with no change (decrease < 25% to increase < 25%, reference), increase NLR at Week 6 by 25–50% and > 75% was associated with poor OS (HR = 1.55 [95% CI = 1.10–2.18] and 2.31 [95% CI = 1.64–3.25], respectively), poor PFS (HR = 1.46 [95% CI = 1.04–2.03], 1.76 [95% CI = 1.23–2.52], respectively), and reduced objective response rate (odds ratios = 0.77 [95% CI = 0.37–1.63] and 0.24 [95% CI = 0.08–0.72], respectively). By contrast, a decrease of 25–50% was associated with improved outcomes. Findings were confirmed in the validation cohort. The study is limited by its retrospective design.
Conclusions: Compared with no change, early decline of NLR is associated with favorable outcomes, whereas an increase is associated with worse outcomes.
Patient summary: We found that the proportion of immune cells in the blood is of prognostic value, namely that a decrease of the proportion of neutrophils-to-lymphocytes is associated with more favorable outcomes while an increase had the opposite effect.

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http://dx.doi.org/10.1016/j.eururo.2016.02.033
0302-2838/

1. Introduction

With the advent of targeted treatments, treatment options for metastatic renal cell carcinoma (mRCC) have changed dramatically [1,2]. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria (also known as Heng criteria) based on clinical (performance status, diagnosis-to-treatment interval) and laboratory (hypercalcemia, anemia, thrombocytosis, neutrophilia) variables are currently used to stratify patients into three risk groups [3].

Inflammation has been recognized as a hallmark of cancer [4] and elevated markers of systemic host inflammation such as C-reactive protein [5] or the neutrophil-to-lymphocyte ratio (NLR) have been shown to be associated with a poor prognosis in several solid tumors [6–8] including RCC [9–11]. The mechanism by which inflammation leads to worse outcomes is not known. Neutrophilia is considered to occur as an inflammatory response and may lead to suppression of cytolytic activity of immune cells such as lymphocytes, natural killer cells, and activated T cells [12,13].

We aimed to confirm that higher NLR is associated with worse prognosis in patients with mRCC and hypothesized that an early decline of NLR during treatment with targeted therapies would indicate a more favorable prognosis independent of established prognostic factors at baseline and that an increase of NLR would be associated with the opposite effect.

2. Patients and methods

Criteria for Reporting Recommendations for Tumor Marker Prognostic Studies were followed where appropriate [14].

2.1. Study populations and data collection

Patients with mRCC receiving targeted therapy at IMDC sites for which NLR data were available prior to first-line treatment, and 6 wk thereafter (±2 wk) were eligible and were analyzed first (IMDC cohort). Patients treated in studies (Supplementary Table 1) conducted or sponsored by Pfizer Inc (New York City, NY, USA) were subsequently analyzed to assess the robustness of the results (validation cohort).

NLR data (the ratio of the absolute neutrophil count to absolute lymphocyte count measured in peripheral blood) were retrospectively collected in the IMDC dataset. In the validation cohort, neutrophil and lymphocyte counts were captured prospectively.

2.2. Statistical analysis

Descriptive statistics for continuous variables are reported as medians and interquartile ranges, and categorical variables as frequencies and percentages. We first analyzed the impact of baseline NLR (log-transformed [lnNLR]) on overall survival (OS) and progression free survival (PFS), defined as time from targeted therapy initiation to death from all causes (for OS) and to progression, treatment cessation, and death (for PFS), censored at last follow-up for those still alive or who have not progressed. Objective response rates (ORRs) were assessed using computed tomography and categorized using Response Evaluation Criteria in Solid Tumors [15,16].

We hypothesized that NLR changes by 6 wk (±2 wk) are of prognostic value. A landmark analysis at 8 wk was done to assess the role of NLR changes, calculated as % change (calculation = [{NLR wk 6/NLR wk 0} – 1]*100) and subsequently grouped into five groups (>75% decrease, 25–75% decrease, no change [<25% decrease to <25% increase], 25–75% increase, >75% increase) with calculation of the hazard ratio (HR) per group. For the landmark analysis, OS and PFS were calculated from 8 wk after targeted therapy initiation. Cox regression models were adjusted for lnNLR at baseline and the six variables in the IMDC score, namely Karnofsky Performance Status < 80%, time from diagnosis to treatment start < 1 yr, corrected calcium > upper limit of normal (ULN), platelet count > ULN, neutrophil count > ULN, hemoglobin < lower limit of normal (for all variables, yes vs no) [3]. Martingale residuals plots were used to verify the linear assumption of the Cox model. Logistic regression models with the same adjustments were used to assess the association of baseline NLR and change in NLR on ORRs. A landmark analysis at 8 wk was also done similarly for "NLR conversion," that is, a change from above to below (or vice-versa) median NLR at baseline rounded to the nearest full integer.

The analyses were subsequently repeated in data from an independent cohort of patients (validation cohort).

Analyses were carried out using SPSS version 20 (IBM Corp. Chicago, IL, USA) and with SAS version v9.2 (Cary, NC, USA). All statistical tests were two sided, and statistical significance was defined as $p < 0.05$. No corrections for multiple significance testing were applied.

3. Results

3.1. Patients

The IMDC cohort comprised a total of 1199 patients who commenced targeted therapy between 2004 and 2013 at nine Consortium sites in the USA, Canada, New Zealand, and Singapore. Baseline characteristics are presented in Table 1. The median age of patients in the IMDC cohort was 62 yr, the majority were men (75%) and treated with sunitinib (74%). Around half of the patients were in the intermediate IMDC prognostic group. One thousand one hundred and sixty six, 1076, and 1058 patients were included in the landmark analysis at wk 8 of OS, PFS, and ORR, respectively.

3.2. Prognostic role of NLR at baseline

Martingale residual plots confirmed linearity of lnNLR and therefore, the Cox model was fitted with lnNLR (Supplementary Fig. 1). Estimated 1-yr and 2-yr survival rates from univariable Cox regression based on the continuous lnNLR are presented in Figure 1A.

Higher NLR at baseline was associated with shorter OS (adjusted HR per 1 unit increase in lnNLR = 1.69, 95% CI = 1.46–1.95, $p < 0.001$), shorter PFS (adjusted HR per 1 unit increase in lnNLR = 1.30, 95% CI = 1.15–1.48, $p < 0.001$), and lower ORR (adjusted OR per 1 unit increase in lnNLR = 0.69, 95% CI = 0.52–0.90, $p = 0.007$).

3.3. Early change in NLR

In the landmark analysis at wk 8, NLR change from baseline to wk 6 (±2 wk) during targeted therapy was an independent prognostic factor for OS and PFS ($p < 0.001$).

Table 1 – Patient and disease characteristics

Variables	N = 1199		N = 4350	
	N	%[a]	N	%[a]
Age at therapy initiation (yr)				
Median	62		59	
Interquartile range	54–70		54–67	
Range	14–89		18–91	
Sex				
Male	895	75	3102	71
Female	304	25	1248	29
Karnofsky Performance Status				
80–100%	825	76	4273	99
<80%	256	24	57	1
Missing	118		20	
Time from diagnosis to targeted therapy				
<1yr	617	52	2569	60
≥1 yr	580	49	1717	40
Missing	2		64	2
Prior systemic therapy				
Yes	0	0	1502	35
No	1199	100	2833	65
Missing data	0		15	
Therapy				
Sunitinib	889	74	1045	24
Sorafenib	185	15	729	17
Pazopanib	34	3	0	0
Axitinib	0	0	638	15
Everolimus-containing	34	3	0	0
Temsirolimus-containing	7	1	636	15
Bevacizumab-containing	31	3	755	17
Interferon	0	0	547	13
Other	19	2	0	0
Start of treatment (yr)				
2004–2006	434	36	1594	37
2007–2009	367	31	1817	42
2010–2013	398	33	939	22
IMDC risk group				
Favorable	206	23	636	17
Intermediate	466	52	1967	53
Poor	217	24	1118	30
Missing data	310		629	
Corrected calcium				
>10 mg/dl	115	11	822	19
≤10 mg/dl	973	89	3490	81
Missing data	111		38	
Hemoglobin				
>LLN	567	48	2285	53
≤LLN	617	52	2061	47
Missing data	15		4	
Neutrophils				
>ULN	130	11	653	17
≤ULN	1069	89	3209	83
Missing data			488	
Thrombocytes (G/l)				
>ULN	208	19	805	19
≤ULN	864	81	3529	81
Missing data	127		16	
NLR baseline				
Median	3.5		3.0	
Interquartile range	2.4–5.1		2.1–4.4	
Missing	0		0	
NLR wk 6				
Median	2.3		2.3	
Interquartile range	1.5–3.8		1.6–3.5	
Missing	0		322	

IMDC = international metastatic renal cell database consortium; LLN = lower limit of normal range; NLR = neutrophil to lymphocyte ratio; ULN = upper limit of normal range.

[a] Due to rounding not all percentages total 100.

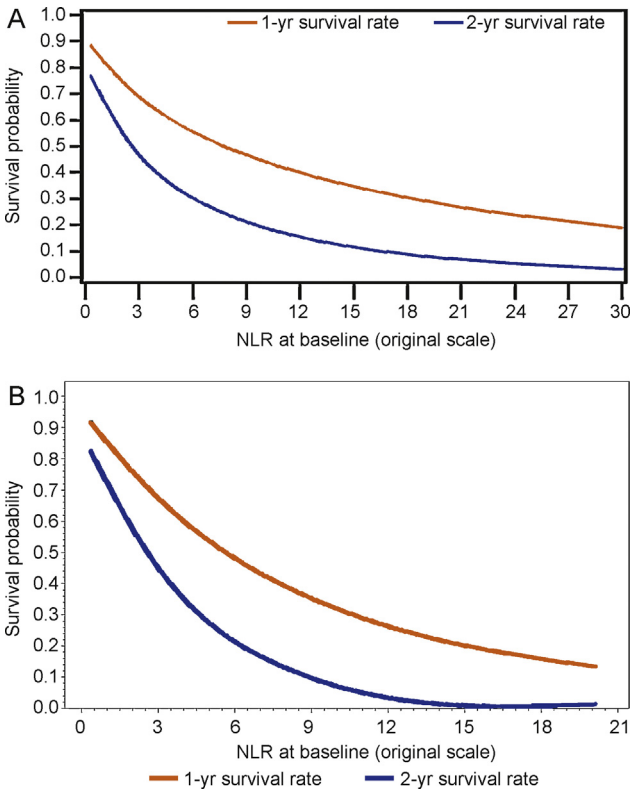

Fig. 1 – Estimated 1-yr and 2-yr survival rate from univariate Cox regression based on the continuous neutrophil-to-lymphocyte ratio (NLR; on the natural logarithmic scale). (A) International Metastatic Renal Cell Carcinoma Database Consortium cohort. (B) Validation cohort.

Compared with no change (decrease < 25% to increase < 25%, reference), increase NLR by 25–50%, and >75% was associated with poor OS (HR = 1.55 [95% confidence interval {CI} = 1.10–2.18], 2.31 [95% CI = 1.64–3.25], respectively) and poor PFS (HR = 1.46 [95% CI = 1.04–2.03], 1.76 [95% CI = 1.23–2.52], respectively). By contrast, a decrease of 25–50% was associated with improved outcomes (Fig. 2, left panels). No significant effect was seen for both endpoints for decrease > 75%, possibly because the sample size is small in that group and some of patients had extremely high baseline NLR. Similarly, we observed better response rates in patients who achieved NLR decrease. The odds ratio (OR) for ORR for decrease > 75% and decrease 25–50%, were 3.53 (95% CI = 1.38–9.01) and 1.70 (95% CI = 1.17–2.45), respectively. The OR for an increase of 25–50%, and increase > 75% were 0.77 (95% CI = 0.37–1.63) and 0.24 (95% CI = 0.08–0.72), respectively, as compared with no change (decrease < 25% to increase < 25%, reference).

NLR decline from > 3 to ≤ 3 by wk 6 was associated with significantly longer OS compared with patients where NLR remained > 3 (adjusted HR = 0.54, 95% CI = 0.51–0.79, $p < 0.001$). In contrast, in patients where NLR increased from ≤ 3 to > 3 by wk 6, there were significantly worse outcomes (HR = 1.97, 95% CI = 1.34–2.90, $p = 0.001$).

Likewise, in patients with NLR > 3 at baseline with conversion of NLR to ≤ 3 by wk 6, PFS was significantly

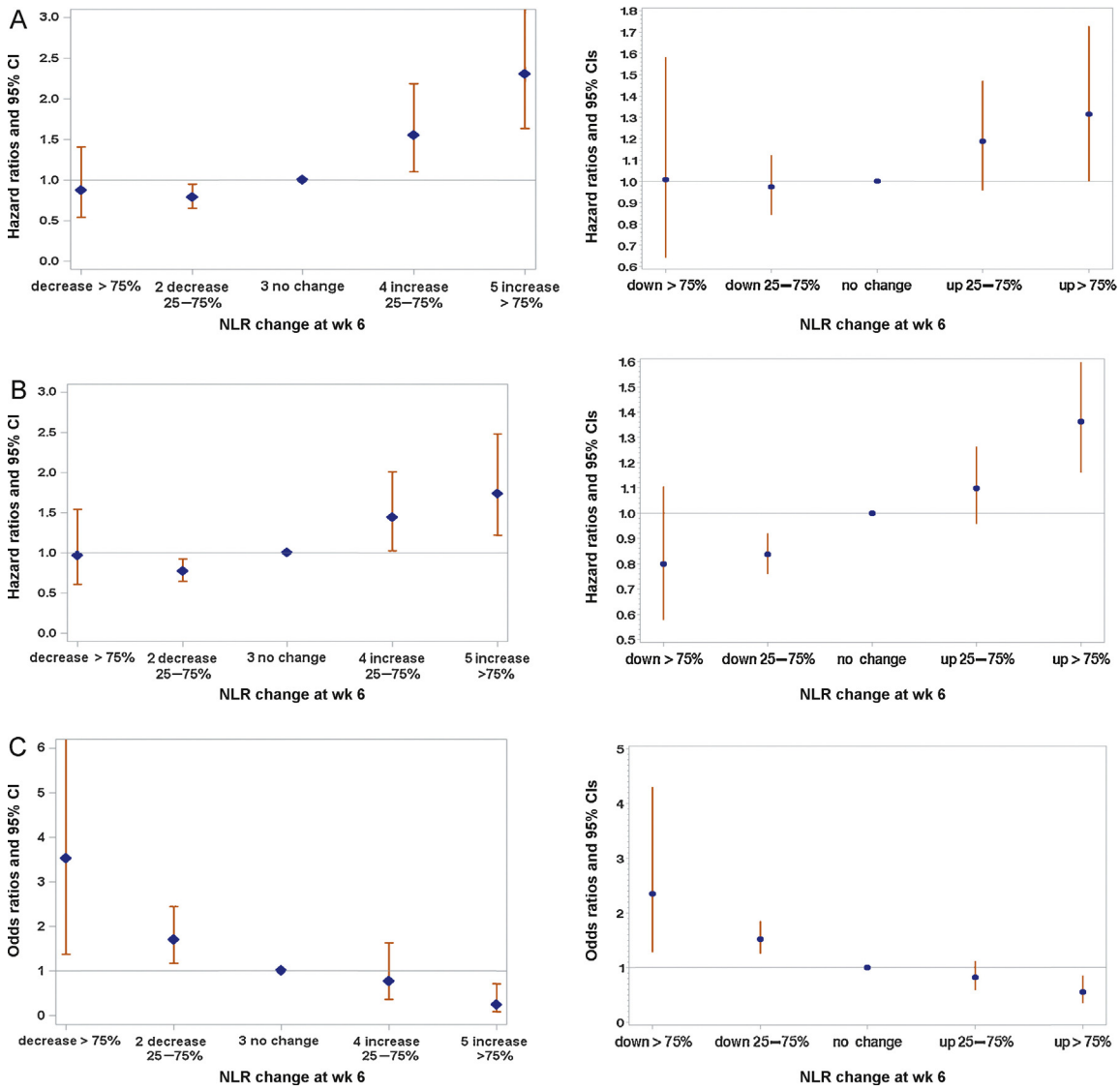

Fig. 2 – Impact of change in neutrophil-to-lymphocyte ratio (NLR) at wk 6 (±2 wk) on (A) overall survival, (B) progression-free survival, and (C) response. Hazard ratios or odds ratios were estimated from multivariable Cox or logistic regression adjusted for baseline LN (NLR) values and International Metastatic Renal Cell Carcinoma Database Consortium risk factors. Overall survival and progression-free survival were calculated from wk 8; "no change" in NLR (defined as –25% to +25%) was used as the reference group in the comparison. Left panels: International Metastatic Renal Cell Carcinoma Database Consortium cohort; right panels: validation cohort.
CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression free survival.

longer compared with patients without such conversion (adjusted HR = 0.62, 95% CI = 0.50–0.77, $p < 0.001$). An increase of NLR from ≤ 3 at baseline to > 3 by wk 6 was associated with shorter PFS compared with patients without such conversion (HR = 1.65, 95% CI = 1.13–2.42, $p = 0.010$).

ORRs were highest in patients with NLR ≤ 3 at baseline that remained low by wk 6 (36.5%), whereas in patients with NLR ≤ 3 at baseline and increase to > 3 by wk 6 ORR was 12.3% (adjusted OR for response OR = 0.23; 95% CI = 0.09–0.62, $p = 0.003$). High response rates were also observed in patients with NLR > 3 at baseline who had a decline to below this threshold by wk 6 (35.4%), whereas in patients with NLR > 3 at baseline where NLR remained > 3 by wk 6 the ORR was 13.0% (adjusted OR = 3.63; 95% CI = 2.20–6.01, $p < 0.001$).

3.4. *External validation*

The validation cohort comprised of 4350 patients treated with axitinib, bevacizumab, interferon-alpha, sorafenib, sunitinib, or temsirolimus in one of 12 prospective clinical trials (Supplementary Table 1). The median age of patients was 59 yr and the majority were men (71%). Around half of the patients were in the intermediate IMDC prognostic group and the median NLR was 2.98 (Table 1).

Overall, the results were similar to those seen in the IMDC cohort. Estimated 1-yr and 2-yr survival rates from

univariable Cox regression based on the continuous lnNLR and for changes by wk 6 are presented in Figures 1B and 2 (right panels), respectively.

4. Discussion

Markers of host inflammation, such as NLR, have gained increasing attention as prognostic markers in solid tumors and in nonmalignant conditions [8]. The influence of baseline NLR and of NLR change during targeted therapy was explored in the present analysis. Data show that an elevated NLR at baseline is an adverse prognostic factor in mRCC with linearity of natural logarithmic NLR and in landmark analyses an early decrease is associated with better outcomes in terms of OS, PFS, and response rates. In contrast, an increase in NLR was associated with unfavorable outcomes. This held true after adjustment for known prognostic factors in mRCC including baseline NLR and was validated in a large cohort of patients treated in prospective clinical trials with different therapies. Although "change in NLR" is a continuous variable, we created groups and also assessed "conversion" from above to below (or vice-versa) baseline NLR of 3 (the median in our cohorts) to facilitate the use in daily practice.

These data suggest that NLR may be a robust response biomarker. If a NLR starts high and decreases by wk 6, this may reassure the treating physician and patient that the therapy is associated with a response and better survival. For example, a patient with stable disease or even slightly growing disease by tumor measurements may find a decline of NLR comforting and thus may stay on the targeted therapy longer. However, like with other dynamic clinical variables of prognostic value as sunitinib-induced hypertension and neutropenia, which have been shown to be associated with improved clinical outcomes [17–19] the opposite, like an increase in NLR or lack of elevated blood pressure alone should not prompt treatment discontinuation but may have utility in the setting of early treatment-related toxicity when the balance between benefit and risks of ongoing therapy is unclear. Baseline NLR may also have utility as a stratification variable especially for immunotherapy agents in development, for example, blockade of programmed cell death protein 1 [20].

Several groups have investigated the role of NLR in RCC but not NLR changes. In a study of nonmetastatic RCC undergoing nephrectomy, pre-operative NLR was significantly associated with recurrence free survival (recurrence free survival rates at 10 yr: 80% and 58% for NLR < 2.7 and ≥ 2.7, respectively) [10]. A further study in nonmetastatic RCC patients found that NLR was an independent prognostic factor for overall survival but not for cancer-specific or for metastasis-free survival [11]. In other small studies of patients with mRCC treated with targeted agents NLR > 3 showed worse outcomes [9,21,22]. Changes in NLR during the early phase of targeted therapy have also been postulated to predict a benefit from subsequent treatment [23].

Despite a rapidly growing body of literature on NLR the mechanism underlying the association of this marker of inflammation remains poorly understood. Kobayashi et al [23] suggested that NLR likely reflects the relative extent of inflammation and host immunity, since its value is directly affected by the total count of neutrophils and lymphocytes, which are major constituents of cancer-related local inflammation and the most effective suppressors of cancer progression, respectively. Smoldering inflammation in the tumor microenvironment has many tumor-promoting effects: it aids in the proliferation and survival of malignant cells, promotes angiogenesis and metastasis, subverts adaptive immune responses, and alters response to antineoplastic agents [24]. The importance of lymphocytes has been highlighted in several studies where increasing infiltration of tumors with lymphocytes has been associated with better responses to cytotoxic treatment and prognosis in cancer patients [25–27]. Lymphopenia has been shown to be an independent predictor of inferior survival in RCC [28]. Taken together, NLR captures both groups as a single measurement and may be an indicator mirroring both neutrophil-dependent protumorigenic inflammation and host immunity driven by lymphocyte function.

This study has limitations. Firstly, this was a retrospective analysis with the potential of selection bias. However, our findings were externally validated in pooled data from prospective clinical trials. Secondly, we could not adjust for other prognostic factors than those included in the IMDC score. Specifically, no data on dose reductions, treatment induced hypertension or hypothyroidism, use of concurrent medication, and metastasectomy that may play a prognostic role (eg, statins), or depth of remission were available [29]. We also could not control for drugs that may influence blood counts (eg, steroids) but aimed not to include patients with known acute conditions other than mRCC that led to neutrophilia and thus an elevated NLR. In the validation cohort, patients with significant comorbidities were excluded according to the trial specific selection criteria. Lastly, as no data from untreated patients were available it was not possible to investigate the interaction between treatment and NLR at baseline or after 6 wk to assess its potential true predictive value, in addition to its prognostic role.

5. Conclusion

NLR is a readily available prognostic factor independent of IMDC criteria. Change in NLR also appears to be a robust early response biomarker.

Results of this study were presented in part at the ESMO conference September 26–30, 2014, Madrid, Spain (poster presentation) and the ASCO Genitourinary Cancers Symposium, February 26–28, 2015, Orlando, FL (oral presentation).

Author contributions: Daniel Y.C. Heng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Templeton, Knox, Amir, Hermanns, Heng.
Acquisition of data: Templeton, Knox, Lawrence, Broom, Fay, Rini, Donskov, Bjarnason, Smoragiewicz, Kollmannsberger, Kanesvaran, Alimohamed, Choueiri, Heng.
Analysis and interpretation of data: Templeton, Knox, Simantov, Lin, Xie, Lawrence, Broom, Fay, Rini, Donskov, Bjarnason, Smoragiewicz,

Kollmannsberger, Kanesvaran, Alimohamed, Hermanns, Wells, Amir, Choueiri, Heng.
Drafting of the manuscript: Templeton, Amir, Heng.
Critical revision of the manuscript for important intellectual content: Templeton, Knox, Simantov, Lin, Xie, Lawrence, Broom, Fay, Rini, Donskov, Bjarnason, Smoragiewicz, Kollmannsberger, Kanesvaran, Alimohamed, Hermanns, Wells, Amir, Choueiri, Heng.
Statistical analysis: Templeton, Xie, Simantov, Amir, Heng.
Obtaining funding: None.
Administrative, technical, or material support: Knox, Simantov, Wells, Choueiri, Heng.
Supervision: Knox, Simantov, Heng.
Other: None.

Financial disclosures: Daniel Y.C. Heng certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Templeton: consultancy (without personal compensation) Sanofi, Astellas, BMS; Knox: research support Pfizer, AstraZeneca; Lin: employment Pfizer, stock ownership Pfizer; Simantov: employment Pfizer, stock ownership Pfizer; Lawrence: travel grant Roche; Rini: consultancy and research funding Pfizer; Donskov: research funding Novartis, GSK, Pfizer; Kanesvaran: speaker bureau Pfizer and GKS, advisory board GSK and Bayer; Choueiri: research funding Pfizer, GSK, Novartis, BMS, Merck, Exilixis, Roche, AstraZeneca, Tracon, and consultancy Pfizer, GSK, Novartis, Merck, Bayer, AstraZeneca; Heng: consultancy Pfizer, Novartis.

Funding/Support and role of the sponsor: None.

Acknowledgments: The authors would like to thank the people involved in maintaining the Consortium database up to date. Templeton's work was supported by a grant from the Swiss Cancer Research Foundation. This work was supported in part by the DF/HCC Kidney Cancer SPORE P50 CA101942-01 to TKC. Funded also in part by the Trust Family, Michael Brigham, and Loker Pinard Funds for Kidney Cancer Research at Dana-Farber Cancer Institute for TKC. The authors also would like to thank all patients for participating in clinical trials and Pfizer for providing access to study databases.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.02.033.

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